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## LII

### THE FUNCTIONS OF THE ROUND WINDOW

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The problem of the service of the round window in the ear's response to sounds was raised by DuVerney<sup>3</sup> in 1683 and has continued ever since as part of the unsettled concerns of the student of hearing. DuVerney supposed this window to be one of the routes of entrance of vibrations into the cochlea, and this idea has persisted, in and out of favor, to the present day.

Lately this problem has received renewed attention in the work of Hughson and his associates<sup>4-8</sup> and their encouragement of a surgical blocking of the window as a measure for the relief of deafness.

Hughson and Crowe<sup>7, 8</sup> first applied the electrical response method to the study of the round window. With cats as subjects and an electrode on or near the auditory nerve, they tested the effects of various kinds of blocking of the window. They observed no changes in the responses as a result of blocking the window with

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From the Princeton Psychological Laboratory. This work was carried out under contract with the Office of Naval Research, as Contract N6-onr-270 Task Order III.

wax or plaster, but reported an enhancement when pressure was exerted on the window with a plug of moist cotton. Later they obtained similar improvements, which amounted to 10 db. on the average, when periosteal grafts were implanted in the round window niche. These improvements were most noticeable over the range 512 to 4096 cycles.

Culler, Finch, and Girden<sup>1, 2</sup> repeated these experiments on dogs, with contrary results. Their technique varied slightly. They filled the round window niche with a plug of soft gum wrapped about with gauze, and attached a thread so that the plug could quickly be drawn out of the niche when desired. Their measurements of the responses during the plugging were followed at once by measurements after the plug was removed. They found invariably a reduction of the responses, which in the more reliable tests amounted to about 10 db. By using also a conditioned response method to test the hearing of the animals with and without the plug, they obtained the same difference of 10 db. in favor of the normal condition.

As a result of further investigations these authors suggested that Hughson and Crowe's results may have arisen through a modification of the electrical conductivity of the tissues due to the application of the moist cotton. The manipulations, they thought, could have provided a more suitable path for the leakage of currents from the cochlea to the electrode remotely located in the region of the nerve. With an electrode in the middle ear, in close contact with the cochlear capsule, the results were various; sometimes they showed an increase and sometimes a decrease, according to the particular procedures followed. These authors concluded that despite these variations in the reception of the electrical changes the actual hearing of the animal was always diminished by the damping or immobilization of the round window membrane.

Hughson continued his investigations with human subjects, and performed some 35 operations designed to improve hearing by immobilizing the round window. At first he approached the round window by the postauricular route, but later worked endaurally, and in either case introduced graft materials into the niche, packing it as firmly as possible without unduly endangering the membrane itself. As a result of this operation, Hughson reported improvements in nearly all cases, and never any impairments. The course of improvement, as he pictured it, was first delayed and then appeared gradually, ending after some weeks in a gain of about 10 db.



It is to Hughson's credit that he made careful and repeated audiogram tests and reported his results fully. Anyone, therefore, is in a position to judge his case. From our study of the results we do not share his optimistic view of the benefits of the operation. It is true some of the trends are clearly favorable, but the amounts of change are small and well within the common variations to which such results are subject: variations due to practice, or altered attitude or other subjective conditions.

The fate of the round window grafts is uncertain. They were under observation during the interval that the opening that had been made in the ear drum was unhealed, and for that time were seen to be still present in the niche. Whether they remained longer and were present at the time the supposed improvements showed themselves, or whether by then they had been absorbed and the ear returned to a normal condition, it is impossible to say.

We have continued the basic study of round window function both to aid in an evaluation of these claims for surgical treatment and to enlarge more generally our understanding of the processes of sound conduction. As in Hughson and Crowe's first work reported here, we have made use of the electrical potentials to determine the effects of the manipulations.

The experiments were carried out on 14 cat ears, with a ventro-medial approach to the auditory bulla, as described earlier.<sup>9</sup> After the bulla was opened an electrode was placed usually on the round window membrane, or sometimes on the cochlear capsule, and the cochlear potentials recorded while stimulating with pure tones. The sound pressure delivered to the ear was accurately determined by means of an acoustic probe which consisted of a Western Electric Type 640 AA condenser microphone provided with a front cap and probe tube, and calibrated as a unit. The amplifying and recording systems were calibrated also to show the magnitude of the response in absolute units.

The general procedure consisted first of measuring the response of the ear to a series of tones under standard conditions with the round window free, then to block it in one of several ways and repeat the measurements, and finally to remove the block and take the measurements once more. The results are presented as the differences in decibels resulting from the blocking. The procedures varied in detail as will be described presently.

A technical problem that arose early in these experiments was the most suitable location for the active electrode. After many

exploratory experiments we have determined that the best location is the round window membrane. We have observed the effects from two different electrodes at the same time, one on the round window membrane and another on the bony capsule, and the pattern of changes resulting from the blocking is the same. However, the greater sensitivity exhibited at the round window and the more constant contact afforded by its moist surface greatly favor this location. The operation of blocking does not interfere seriously if the electrode is a narrow strip of thin platinum foil and is placed along the bony lip of the niche and bent down one wall in such a manner as to make contact with the edge of the membrane below. With care a plug then can be placed without any disturbance of the electrode. Removal of the plug rarely carries the foil out as well, but in any case replacement is a simple matter.

In this connection we recall the suggestion made by Culler and his associates that the changes found in the cochlear potentials are the results of variations in the conductivity of the tissues between the electrode and the place of origin of the potentials. Our observations showed no such variations. However, as mentioned in particular below, we were careful to use nonconducting prods and plugging materials. Their suggestion might well apply to metallic applicators and moist cotton pledgets.

*Series 1.* Our immobilization of the round window membrane has taken a number of forms. The simplest is the manual application of a probe to the membrane. The probe was small and made contact with about the central half of the membrane's surface. It was applied with sufficient pressure to give a noticeable indentation. If this is done while observations are made of the responses to a continuing sound, not the slightest effect is seen. Increasing the pressure within the range that the membrane is capable of withstanding without rupture had in some cases a very slight effect tending to decrease the response.

In carrying out this experiment, two precautions are necessary. The probe must be a nonconductor to avoid short-circuiting the potentials. Ours was made of lucite. Also, its shank must be thin to avoid a disturbance of the sound field.

We would emphasize here that in all these experiments a possible disturbance of the sound field is always to be kept in mind. It is remarkably easy, on inserting various things into the middle ear cavity, and especially about the drum, to cause wide variations in the sound field and thereby to produce all sorts of alterations in the

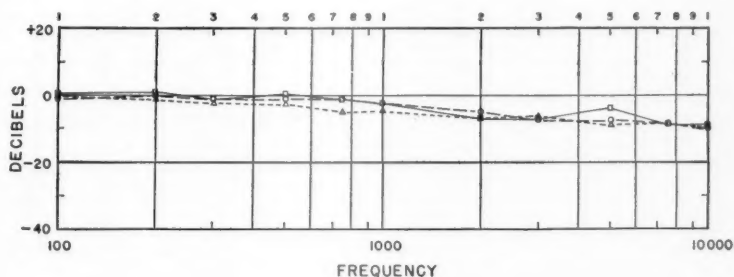


Fig. 1.—Effects of occlusion of the round window by means of a narrow tube. The zero line represents the normal condition, before the tube was applied.

responses, largely of an unpredictable kind. The changes are reproducible in a given animal but vary considerably from one animal to another. Probably they reflect anatomical peculiarities.

*Series 2.* In a second method an air-tight tube was sealed over the round window and various degrees of air pressure were applied to the membrane, thus testing some of the earlier observations of other investigators and obtaining a measure of the blocking effect. The system devised to produce this pressure consisted of a hand bulb with an air escape valve attached by rubber tubing to a glass Y tube, one branch of which went to a manometer and the other to a lucite tube made to fit over the round window. The lucite tube was 100 mm. long and 2 mm. in outside diameter and had a bore equal to the size of the round window niche. It was tipped with rubber to afford an air-tight seal with the niche, and was held by hand. About 12 feet of rubber tubing were used in the connections. In this procedure the ear was intact except for the bulla opening, and the sounds were delivered to the drum through the usual sound tube inserted tightly into the external auditory meatus. The acoustic probe accompanied this tube and recorded the sound pressures adjacent to the drum.

It was found that merely placing the pressure tube tightly over the niche with the other end open to the air (termed the zero pressure condition) reduced the response slightly to the high tones. The tests were repeated on several different ears and the same pattern was consistently produced. Fig. 1 shows the results obtained on three animals. Each curve represents the loss in response from

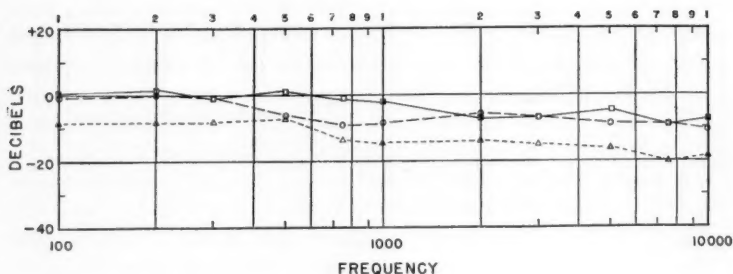


Fig. 2.—Introduction of an air pressure of 25 mm. of mercury through the occluding tube.

the normal brought about by placing the hollow tube over the window. The departure from the normal seems to start around 500 cycles and to increase regularly as the frequency rises, with a maximum loss of around 10 db. at 7500 and 10,000 cycles.

With the tube held in position, the introduction of an air pressure of as much as 25 mm. of mercury had no certain effect beyond that already caused by the simple application of the tube. In Fig. 2 the same three ears are again shown, now under a positive pressure of 25 mm. of mercury. It will be noted that one curve depicts a loss of 9 db. for the low tones and an average loss of 15 db. for the high tones. The general pattern of this curve, however, still resembles the other two, and it is possible that a general change in sensitivity of about 9 db. followed the application of pressure on account of a shift in the position of the electrode. If we subtract such an amount we have in this ear, as in the others, a simple high tone loss of about 6 db.

*Series 3.* A third method of immobilizing consisted of packing the niche with bone wax, usually with a few cotton fibers intermingled to make it easier to remove the plug as a unit. In this procedure the plug was pressed in by a mechanically held lucite obturator so that the plug would make intimate contact with the membrane. On extraction the plug showed clearly the form of the niche. Accordingly we consider the immobilization to have been extreme, if not complete. The ear was intact and an acoustic probe tube inserted into the meatus as in Series 2.

The results of this procedure varied somewhat in different animals, but typically took the form shown in Fig. 3. The same ears

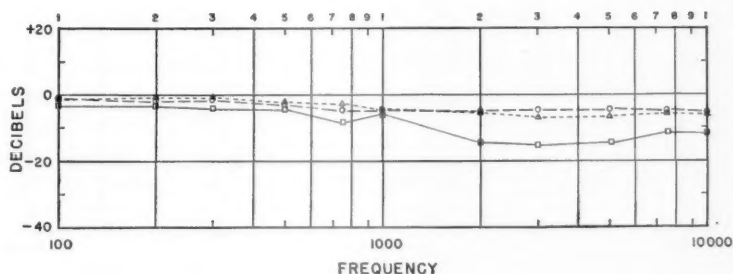


Fig. 3.—Effects of plugging the round window niche with wax, when the middle ear apparatus was intact.

as shown in the previous figures are shown here. The responses suffered a small general impairment though only in modest degree. The depression varied with frequency, usually, as shown by two of these ears, from 1 or 2 db. at the lower end to 4 or 5 db. at the higher end. In the third ear shown (which represents an extreme case), the loss amounted to as much as 17 db. for the higher tones.

During this series the round window niche of one animal, not shown in the figure, was filled with mercury. The results of this procedure were the same as shown in Fig. 3.

Since all these procedures, the 'zero pressure' condition, the application of a severe positive pressure, and a mechanical blocking of the round window, had similar effects upon the responses, we had to raise anew the possibility already mentioned that the tube or obturator was interfering in some way with the sound field. To test this possibility the lucite obturator was placed almost in its usual position, but with its end just out of contact with the round window. No effect on the responses was observed.

A second possibility, in line with DuVerney's ancient conception, was that there is ordinarily a certain amount of sound entering the cochlea by way of the round window and that the plug or lucite tube acts as a barrier to it. To hold this view in the presence of these results it is necessary to suppose that any such sound is effectively out of phase with that entering the cochlea by the ossicular route, and it thereby aids the principal path of conduction. Then its removal would be a handicap. However, a little consideration

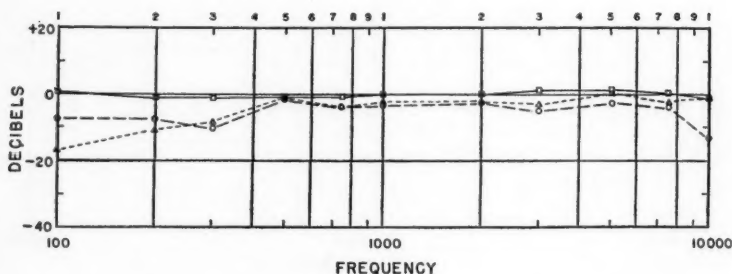


Fig. 4.—Effects of plugging the round window niche with wax after removal of the drum and ossicles. The zero line represents the sensitivity after the middle ear operation, but with the round window free.

makes it appear quite unlikely that this is an explanation of the observed results. In the first place, if sound were entering the two windows with equal intensity and  $180^\circ$  out of phase, the maximum increase in response that could be expected would be 6 db., for if the waves supplemented each other at the two ends of the system no more than a doubling of the pressure could result. Yet we know<sup>9</sup> that the sound getting into the inner ear by way of the ossicular chain and the oval window is about 28 db. greater than that entering the round window. Accordingly the maximum reinforcement that the sound can produce at the round window, assuming the most favorable phase difference of  $180^\circ$ , is the negligible quantity of 0.4 db.

A third possibility neglects any secondary entrance of sound and considers only an effect upon the cochlear mechanics. Blocking the window may alter the mobility of the cochlear fluids and thereby impair the normal responses. The following experiment explores this possibility further.

*Series 4.* The lateral wall of the tympanic cavity was dissected away and the drum and outer ossicles removed. Sometimes the stapes was left intact in the oval window; at other times its crura were removed and only the footplate remained. Then the sound tube was sealed over the oval window, along with the acoustic probe, and the stimuli delivered directly to this site. No secondary conduction of sound to the round window then could occur. A blocking of the round window thereupon was carried out with

results as shown in Fig. 4. Here the curves again represent the amount of loss in response due to the blocking.

Under these conditions the tendency for the high tones to be more greatly depressed has disappeared. Instead there may be a slight loss of 2 or 3 db. throughout the entire range, although one ear showed hardly any effect. As shown, two of the ears suffered a more marked loss for the low tones, but the third failed to follow this pattern.

In view of these results, it would seem that the losses appearing as the result of isolating or immobilizing the round window somehow are related to the presence of the normal middle ear system. We have already ruled out phase effects and disturbance of the sound field as possible causes. Evidently the changes are a result of an alteration of the mechanical state of the responsive system. The parts set in motion, including drum, ossicles, cochlear fluids, sensory structures, and the round window, form an intercoupled acoustic mechanism, and a mechanical alteration of one part is reflected in the whole.

The nature of the mechanical change resulting from our treatments of the round window is rather difficult to infer. The matter is complicated by the fact just established that the change has a different result depending on whether the middle ear is present. If we accept the risk of over-simplifying the problem and regard it as the facts now seem to demand, we have a formulation as follows:

When the middle ear is present, the loading of the round window by any of the methods described has the effect of adding mass to the responsive system, for it progressively reduces the high tones and leaves the low tones unaltered. On the other hand, when the middle ear is absent the same treatment, if it does anything, chiefly impairs the low tones, and so has the effect of adding stiffness to the responsive system. To make this formulation meaningful we suppose (contrary to usual expectations) that the middle ear contributes greatly to the stiffness of the cochlear system and less significantly to its mass. If that is so, the stiffness added by blocking is negligible when the ear is intact, and then the blocking chiefly contributes to the mass. On the other hand, when the middle ear is absent the stiffness afforded by the blocking looms large. This supposition is consistent with the fact reported in an earlier study<sup>9</sup> that removal of the middle ear affects most seriously the high tones.



On account of its complexity it is not possible now to conceptualize further the normal behavior of the responsive system or the changes caused by the blocking procedures.

#### SUMMARY

The function of the round window was studied by immobilizing it in various ways while recording the electrical potentials of the cochlea. The effects vary both with the method of immobilizing and with the condition of the ear. When the ear is intact, and the sound stimulus is directed at the ear drum in the usual way, a partial immobilization of the round window membrane by applying a prod to its surface had no measurable effect. Under the same conditions, applying a tube over the window, exerting a heavy air pressure on it, and plugging the niche with wax all had nearly the same effect, which was a progressive reduction of the response to high tones, amounting at the most to about 10 db. When the middle ear was removed and the sounds were introduced through a tube sealed over the oval window, the same procedures had little or no effect on the responses to high tones, but in some ears reduced the responses to low tones. Possibilities are considered for the explanation of these results. Check experiments seem to exclude a disturbance of the sound field as a result of the manipulations. Also ruled out is the possibility that the results can be accounted for as a modification of a secondary path of sound transmission by way of the tympanic space and the round window. Such transmission can have only negligible effects. We are left with the conclusion that the blocking affects the mechanical impedance of the ear.

A surprising result is that all our forms of blocking, whether partial or complete, cause only minor alterations of the sensitivity. The changes occur mostly at one end or the other of the frequency scale, and are usually of the order of 5 db., rarely exceeding 10 db. These changes are deleterious. It plainly follows that there is no warrant for the use of an immobilizing procedure in clinical practice, as Hughson proposed. The introduction of grafts into the round window, according to these observations, can be of no benefit to hearing.

The calibrated condenser microphone was kindly loaned by the Bell Telephone Laboratories.

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### LIII

## ELECTROCOAGULATION OF THE MEMBRANOUS LABYRINTH

EXPERIMENTAL HISTOLOGICAL STUDIES  
IN THE MONKEY

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In recent years the histological studies of Hallpike and Cairns,<sup>9</sup> Altmann and Fowler,<sup>1</sup> and Lindsay<sup>10</sup> have indicated that Ménière's disease is a syndrome of the vestibular end-organ and not a disease of the vestibular nerve. As a result, recent surgical techniques have been directed toward the end-organ and away from the eighth nerve.

In 1927 Portmann<sup>12</sup> proposed an operation on the end-organ for the relief of symptoms in Ménière's syndrome. Since then there have been various techniques advocated by Putnam,<sup>13</sup> Berggren,<sup>2</sup> Mollison,<sup>11</sup> Cawthorne,<sup>3,4</sup> Wright,<sup>14</sup> and Goodyear.<sup>8</sup>

Among the procedures using the principle of destruction of the labyrinth has been Day's technique of passing a fine needle through a trephine opening in the lateral semicircular canal and coagulating the membranous labyrinth. This procedure has stimulated interest because of its relative simplicity and its uniform results in eliminating the vertiginous attacks.

Although hopeful of saving hearing in his earlier cases, Day has later stated that he could not report good results in the preservation of hearing. Some of the patients that he had previously reported as having usable hearing in the operated ear continued to lose that hearing gradually until there was complete deafness. This experience was also encountered in later cases. In one case of his

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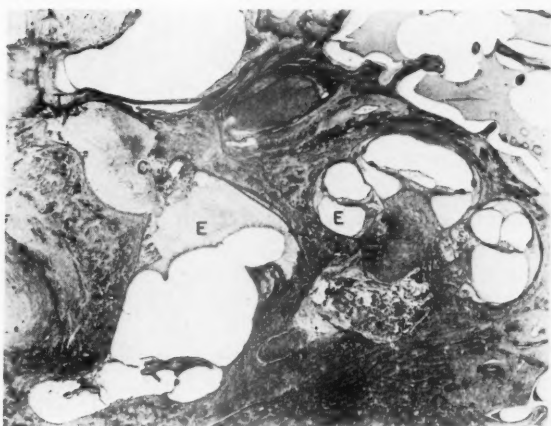


Fig. 1.—Monkey 3, left ear. Section through trephine opening of horizontal semicircular canal showing destruction of the membranous labyrinth, a serofibrinous exudate partially filling the vestibule and extending into the scalae vestibuli and tympani, and dilatation of the cochlear duct in all turns. *T*—trephine opening; *C*—crista of horizontal semicircular canal; *E*—exudate.



Fig. 2.—Monkey 1, left ear. Section through trephine opening showing vestibule almost completely filled with dense fibrous tissue and new bone. Cochlea undamaged. *T*—trephine opening; *A*—ampulla of horizontal semicircular canal; *V*—vestibule; *B*—new bone.

series, however, the hearing, which showed an average loss of 70 decibels before operation, improved to within normal limits postoperatively and has remained so for four years. This fact has convinced Day that eventually his operation can be so modified as to give a better prognosis for the maintenance and improvement of hearing.

The purpose of the experiments presented in this paper has been to demonstrate the histological changes occurring as a result of coagulation of the membranous labyrinth and to determine, if possible, any variation of technique which might improve the prognosis for hearing.

Five monkeys (*Macacus rhesus*) were used, all weighing approximately seven and one-half pounds (3.4 kg.). Anesthesia was induced by intravenous injection of pentobarbital sodium.

The operative procedure paralleled Day's technique as closely as possible and was as follows: Using the postauricular approach a partial simple mastoidectomy was performed exenterating the mastoid cells sufficiently to obtain adequate working space. The mastoid antrum was opened widely. The outer wall of the aditus was removed to expose the incus. With a small motor-driven burr, a trephine opening was made in the horizontal semicircular canal just above and medial to the short process of the incus. Through this opening a fine needle was passed through the canal into the vestibule. Using a portable Bovie electrosurgical unit a coagulating current of an estimated duration of one second was applied and repeated within ten seconds. The needle was then withdrawn and the wound closed with dermalon sutures.

The animals were killed 10 to 40 days after operation by decapitation and the temporal bones placed in Heidenhain's solution within five to ten minutes.

The extent of the operative lesion was determined by histological examination. The temporal bones were sectioned serially in a horizontal plane with an anterior tilt of 30 degrees. A Masson stain was used.

The seven ears operated on are divided into two series. In the first series, a constant current of a dial setting of 20 was used. These animals were sacrificed at appropriate intervals to show the pathology after 10, 20, 30, and 40 days. In the second series, the current was varied from a dial setting of 10 to a dial setting of 40 and all of these animals were killed 30 days postoperatively.



Fig. 3.—Monkey 1, left ear. Section through oval window. Horizontal semicircular canal filled with fibrous tissue and new bone. HC—horizontal semicircular canal; S—stapes; B—new bone; FT—fibrous tissue; VII—facial nerve.



Fig. 4.—Monkey 1, left ear. Round window free. Perilymphatic space of posterior semicircular canal filling in with new bone. R—round window; PC—posterior semicircular canal.

## DATA OF OPERATIONS

Series No. 1. Current: the same; number of postoperative days: different.

Serial No. of Animal	Side	Dial Setting	No. of Post-op Days	Remarks
3	Left	20	10	
2	Left	20	20	Developed laby- rinitis
1	Left	20	30	
3	Right	20	40	

Series No. 2. Current: different; number of postoperative days: the same.

4	Right	10	30	
1	Left	20	30	Same ear as used in Series 1
4	Left	30	30	
5	Left	40	30	Developed laby- rinitis

During the course of the operations, technical difficulties were encountered in two of the ears (Monkey 2, left ear and Monkey 5, left ear). Both of these ears developed a labyrinthitis postoperatively for which an adequate explanation was found on histological examination: (1) pathway produced unintentionally between external canal and mastoid cavity, and (2) tympanic perforation serving as an avenue of infection. They are, therefore, not being included in the series.

Microscopical findings in the remaining five ears showed the following:

*Series 1:*

Monkey 3. Left ear (10 days postoperative—dial setting 20). The mucous membrane of the middle ear showed some edema. The mastoid cavity was filled with fibrous tissue with some regeneration of new bone. The membranous labyrinth was destroyed and the vestibular space was partially filled with a serofibrinous exudate. There was no bone formation in the vestibule nor in the vicinity of the oval or round windows. Both the perilymphatic and the endolymphatic spaces of the semicircular canals were partially filled with a serofibrinous exudate. In the cochlea the vestibular and tympanic scalae contained a serofibrinous exudate. The cochlear duct was dilated in all the turns. There were degenerative changes of the stria vascularis, tectorial membrane and the organ of Corti (Fig. 1).

Monkey 1. Left ear (30 days postoperative—dial setting 20). Except for insignificant changes due to the operation the middle





Fig. 5.—Monkey 3, right ear. Section through ampulla of horizontal semicircular canal and vestibule showing dense fibrous tissue, new blood vessels and new bone filling vestibule. C—crista of horizontal semicircular canal; FT—fibrous tissue; B—new bone.



Fig. 6.—Monkey 3, right ear. Section showing turn of cochlea nearest vestibule. All component cells of organ of Corti are gone. The spiral ligament is degenerated and partially replaced by new bone. V—vestibule (filled by fibrous tissue).

ear was normal with some regeneration of bone in the mastoid cavity. The membranous labyrinth of the vestibule was entirely destroyed, the cavity of the vestibule being filled almost completely by dense connective tissue and new bone formation. The semicircular canals were filled with fibrous tissue and new bone. The round window and the cochlea appeared essentially normal (Figs. 2-4).

Monkey 3: Right ear (40 days postoperative — dial setting 20). The middle ear was normal. The membranous labyrinth of the vestibule was completely destroyed and the vestibular space was filled with dense fibrous tissue, new blood vessels and newly formed bone. Extensive formation of new bone was seen throughout the semicircular canals. There was newly formed bone in the vicinity of the oval window. The membrane of the round window was covered by a plate of new bone. The cochlea appeared normal with the exception of an area at the end of the first turn and at the beginning of the second turn where the spiral ligament showed fibrous degeneration and was partially replaced by new bone. In this same limited area the mesothelial cells of the basilar membrane and the cells of the entire organ of Corti were absent. The cochlear duct appeared dilated in the first turn (Figs. 5-8).

*Series 2:*

Monkey 4. Right ear (30 days postoperative — Dial setting 10). The middle ear was normal except for some changes due to the operation. The perilymphatic space of the vestibule was partially filled with a serous and serofibrinous exudate. The membranous labyrinth was practically unchanged. The macula of the utricle and the saccule, as well as the cristae of the semicircular canals, the round window and the oval window appeared undisturbed. A small amount of precipitate was found only in the scala vestibuli of the cochlea. No degeneration was seen in the organ of Corti or the stria vascularis. There was no hydrops of the cochlear duct (Figs. 9, 10).

Monkey 1. Left ear (30 days postoperative—dial setting 20). The findings are described above (Figs. 2-4).

Monkey 4. Left ear (30 days postoperative—dial setting 30). The middle ear appeared normal except for a small amount of serosanguineous exudate. The membranous labyrinth was destroyed and the vestibular space was predominantly filled with a serous exudate. A small amount of fibrous tissue and new bone was also seen in the vestibule. The round and oval windows appeared normal.



Fig. 7.—Monkey 3, right ear. New bone forming in vicinity of oval window. S—stapes; V—vestibule; B—new bone.

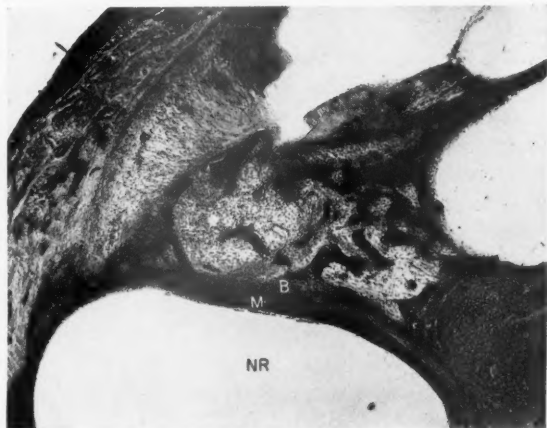


Fig. 8.—Monkey 3, right ear. Section through round window showing membrane covered by new bone. NR—niche of round window; M—membrane of round window; B—new bone.

The semicircular canals were largely filled with a serous exudate. The scalae vestibuli and tympani of the cochlea were also filled with a serous exudate. There was a slight degree of hydrops of the cochlear duct. The organ of Corti, the tectorial membrane and the stria vascularis showed only slight degenerative changes (Figs. 11, 12).

*Comment.*—When an adequate coagulating current was used the membranous labyrinth was consistently destroyed. The nature of the reaction occurring as a result of damage to the vestibule by coagulation is a serous exudate followed rapidly by a serofibrinous exudate which in time becomes organized fibrous tissue. The fibrous tissue may change to new bone which ultimately fills the labyrinthine space. The extensive formation of new bone within the labyrinth might be more definitely demonstrated if these animals were allowed to live from three to six months or longer. The end-point of this reaction was not followed to completion because the process of healing of the inner ear, following damage, is well known.

Changes within the cochlea varied from absence of any damage to a serous and serofibrinous exudate filling both the scalae vestibuli and tympani. Associated with the exudation were varying degrees of atrophy of the functional elements. In some cases there may be initial blockage preventing the inflammatory reaction from passing from the vestibule to the cochlea. Whether this occurs to some extent in all ears, with reversible changes in some cases, must remain speculative. In the right ear of Monkey No. 3 (Figs. 5-8) the localized damage to that part of the cochlear turn nearest the vestibule and to the round window would seem best explained by their proximity to the heat caused in the vestibule at the time of coagulation.

In the light of Day's expressed hope that eventually this operation can be so modified as to give a better prognosis for the maintenance and improvement of hearing the question naturally arose: Can useful hearing be possible when the vestibule is filled with fibrous tissue and bone, even in those cases where the cochlea remains normal? In the right ear of Monkey No. 3 (Figs. 5-8), although the cochlea is undamaged except for a small segment of that portion nearest the vestibule, perilymph-transmitted sound would obviously be impossible because of immobilization of both the oval and round windows by the formation of new bone. In another ear, Monkey No. 1 (Figs. 2-4), on the other hand, we have all the results from Day's procedure of coagulating the membranous labyrinth which might be desired. The membranous labyrinth was

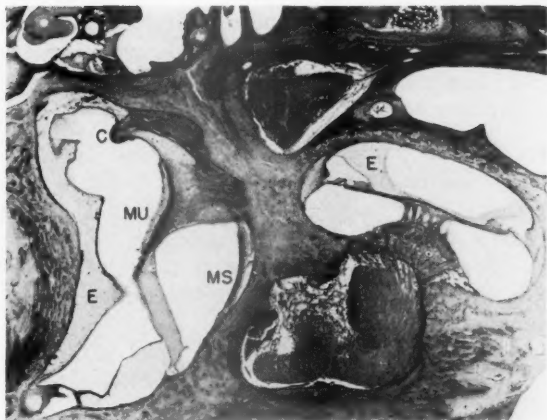


Fig. 9.—Monkey 4, right ear. Section through ampulla of horizontal semicircular canal showing undamaged end-organs. Serofibrinous exudate in perilymphatic space. Serous exudate in scala vestibuli. C—crista of horizontal semicircular canal; MU—macula of utricle; MS—macula of sacculus; E—exudate.

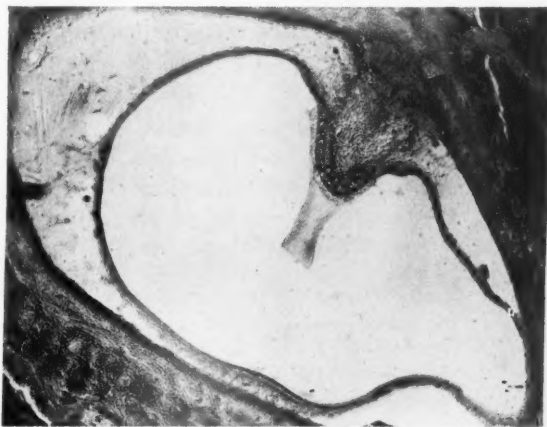


Fig. 10.—Monkey 4, right ear. Undamaged crista of superior semicircular canal.

destroyed. The cavity of the vestibule, 30 days postoperatively, was filled by dense connective tissue and new bone. The round window was entirely free. The cochlea appeared normal. Can sound reach the cochlea? It would be difficult to understand how except through the round window.

Before dismissing the possibility of useful hearing following coagulation of the membranous labyrinth it might be well to point out, nevertheless, that hearing may still be possible by way of the round window when movement has not been impaired by bone formation. Sound might also be transmitted by bone conduction. But hearing by either of these mechanisms would probably require intense sounds.

#### SUMMARY AND CONCLUSIONS

Seven ears in five monkeys were operated on according to Day's procedure which consists of exposing the horizontal semicircular canal, inserting a needle through a trephine opening, and destroying the contents of the vestibule with a coagulating current.

The animals were killed 10 to 40 days after operation and the results determined by histological examination.

In all seven ears healing occurred by primary intention. Labyrinthitis was found in two ears. On study of the sections an adequate explanation for the origin of the infection was discovered in each case.

The remaining five ears were free of infection. In four of these ears a current with a dial setting of 20 or more was applied and the membranous labyrinth was completely destroyed. In the fifth ear, in which the current was reduced to a dial setting of 10, the utricle and the saccule were incompletely destroyed and the semicircular canals were not damaged.

Healing of the labyrinth occurred by fibrosis with progressive changes to bone formation.

There was no significant pattern in the series as to the amount of damage to the cochlea, either related to time elapsed since the operation or to the amount of coagulating current used. The cochlea appeared normal in one ear. In a second ear the cochlea showed only localized damage to the organ of Corti and the spiral ligament immediately adjacent to the vestibule. In three ears there were varying degrees of exudate in the lymphatic spaces and damage to the functional elements of the cochlea.

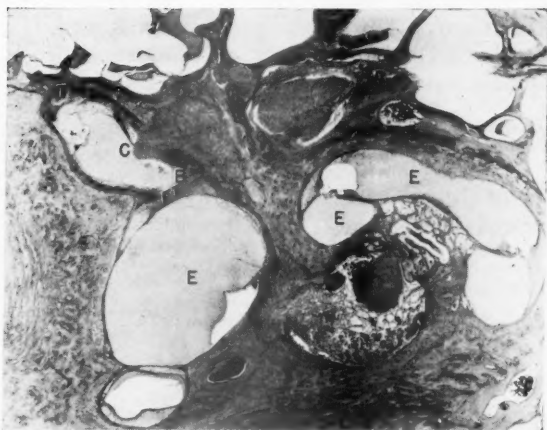


Fig. 11.—Monkey 4, left ear. Section through trephine opening of horizontal semicircular canal showing destruction of end-organs and filling of vestibule with serous exudate, newly forming fibrous tissue and bone. Scalae vestibuli and tympani are filled with serous exudate. *T*—trephine opening (filled in with new bone); *C*—crista of horizontal semicircular canal; *FT*—fibrous tissue; *B*—new bone; *E*—exudate.

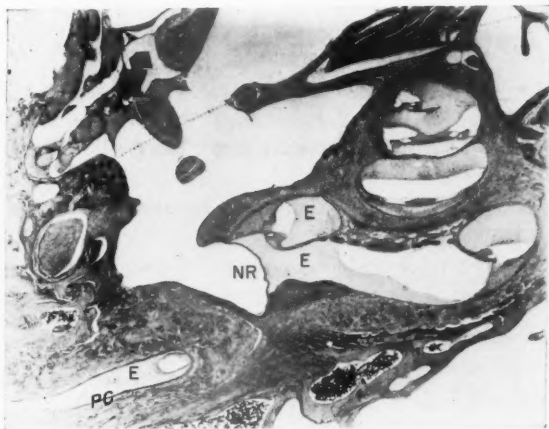


Fig. 12.—Monkey 4, left ear. Section through round window. Perilymphatic space of posterior semicircular canal, scala vestibuli and scala tympani filled with serous exudate. *NR*—niche of round window; *PC*—posterior semicircular canal; *E*—exudate.



The damage to the membranous labyrinth of the vestibule and the semicircular canals, where optimum current is used, is complete and predictable. A uniform result of elimination of vertigo in Ménière's disease may be expected with this procedure.

The damage to the cochlea is unpredictable. Retention of serviceable hearing following this operation is improbable.

In none of the ears was there found by microscopic examination any evidence of damage to the facial nerve.

Grateful acknowledgement is made to Miss Dorothy Linden for the preparation of the histological material.

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LIV

THE DEVELOPMENT OF THE AUDITORY OSSICLES, THE  
OTIC CAPSULE AND THE EXTRACAPSULAR TISSUES

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Various phases of an otological investigation, pursued divisionally, have already been described in a series of journal articles. Now, for the first time, the authors are able to follow concurrent steps in morphogenesis and, as a consequence, to report upon the important steps in the development of the ossicles, the otic capsule, and the portions of the temporal bone which come to surround the capsule. In concluding their presentation, features in the developmental history of the capsule and the stapes will be compared with those which mark the formation of a typical skeletal element, the human tibia.

The observations herein recorded are based upon a study of approximately 300 series of sections, chiefly in the collections at the University of Wisconsin and at the Northwestern University Medical School. Representative specimens are employed for illustra-

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From the Department of Anatomy of Northwestern University Medical School (Contribution No. 494) and from the Department of Anatomy of the University of Wisconsin. This study was conducted under the auspices of the Central Bureau of Research of the American Otological Society. During the course of the investigation Dr. Cauldwell served on a fellowship endowed by the late George J. Dennis, M.D., and subsequently by Mrs. Dennis.

Paper read at the April 1948 Meeting of the Chicago Laryngological and Otological Society and (by invitation) at the Eighty-First Annual Meeting of The American Otological Society, Hot Springs, Va., April 12-13, 1948. The subject matter was also presented, in brief form, at the Sixty-First Annual Meeting of the American Association of Anatomists, Madison, Wis., April 21-23, 1948 (abstract, *Anatomical Record* 10:4, April 1948).

tion; additionally, graphic plates serve as pictorial summaries of the authors' conclusions.

In general it may be said that maturity, in gross form and size and in histological structure, is attained by the ossicles and the otic capsule far earlier than was once believed. In fact, so rapid is development that adult dimensions and configuration of the ossicles and capsule are attained when the fetus has reached the middle of its intra-uterine existence. Equally remarkable is the fact that morphogenesis takes place in surges, some phases of which are so unconventional as to approach the unique.

In earlier articles the authors traced certain phases of the formative process in the capsule<sup>13-23</sup> and in the auditory ossicles,<sup>1-6, 9-12, 24, 26</sup> paying particular attention to the stapes. Several of the figures in the present set have been adapted from these sources.

#### CAPSULE AND EXTRACAPSULAR TISSUES

The osseous otic capsule differs from other bones of the human skeleton in respect to form, structure and function. It houses the sensory organs of hearing and equilibrium; it is a box whose contributory elements fuse completely to form a single bone—thus being unlike the cranium which is made up of many elements separable at sutures. Unlike flat, or membrane, bones and different from long, or cartilage bones, ossification of the capsule takes place at numerous (14) sites. In flat bones, as will be recalled, ossification begins at the center and progresses toward the periphery; in long bones ossification begins in the middle of the shaft (at a diaphyseal center), wherefrom it spreads toward the ends, to fuse ultimately with centers at epiphyseal lines which remain more or less distinct throughout life.

Whereas, in adult bones generally, cartilage of nonarticular location is a rarity, in the capsule numerous small remnants of altered chondral tissue remain prominent throughout the individual's lifetime; these islands of cartilage, surrounded by endochondral bone, form the so-called intrachondrial bone. Cartilage persists also as a partial lining for the fissular tract anterior to the vestibular window (fissula ante fenestram) and for the inconstant tract of shorter course situated posterior to the window (fossula post fenestram).<sup>8</sup>

*Types and Layers of Bone in the Otic Capsule.* The otic capsule is composed of three layers of bone, namely, the periosteal, the intrachondrial combined with the endochondral, and the endosteal. These require separate description.

*Outer layer* (periosteal bone). This is formed from the cambium layer of the periosteum around the cartilaginous capsule. It is like the periosteal bone found in long bones.

Formation of the outer layer begins in the fetus of 126 mm.<sup>†</sup> (16½ weeks). It develops rapidly between the 16th week (126 mm.) and the 27th week (246 mm.); thereafter and to the 40th week (term) there is little increase in size. The otic capsule may be considered to include not only the inner and middle layers, but also that part of the outer layer (periosteal bone) which develops rapidly between the 16th and 27th weeks (126 mm. to 246 mm.). Subsequent growth of the periosteal bone is slow; that part of it which is thus added, during late fetal and early infantile period, may be regarded as being extracapsular; it is less compact and is located in the antral and apical regions.

*Inner layer* (endosteal bone). This layer is always thin and fairly uniform. It is derived from the endosteum, or inner periosteum, and immediately surrounds the labyrinthine spaces.

*Middle layer* (intrachondrial and endochondral bone). This is the fundamental stratum. It is composed of islands of altered cartilage which become surrounded by endochondral bone. Its developmental and structural features distinguish the capsule from other bones of the human body.

Intrachondrial bone consists of irregular areas of calcified hyaline cartilage containing true bone within its lacunae.\* This intrachondrial bone forms the basis upon which endochondral bone is gradually deposited, with the result that ultimately bone marrow is virtually replaced.\*\* The separate sites of ossification within the lacunae of the old cartilage represent the "globuli ossei."\*\*\*

<sup>†</sup>All measurements record crown-rump (CR) length.

\*Several synonymous terms have been applied to the intermediate type of bony tissue described by Bast as "intrachondrial". "Calcified cartilage rests" and "calcified cartilage islands" are found in the older literature, particularly from German sources, and occasionally appear in recent accounts; "cartilaginous interglobular spaces" was introduced by Manasse<sup>27</sup> and persists in French publications. The term "chondroid bone" has recently been used by Zawisch<sup>28</sup> to describe persistent calcified cartilage in the osteogenesis of marble bone disease.

\*\*Small areas may remain around blood vessels (see Fig. 1b).

\*\*\*The separate ossification foci occurring about and within cartilage lacunae persistent islands of calcified cartilage (or intrachondrial bone) were originally described by Brandt<sup>25</sup> as "globuli ossei." This descriptive term has been frequently misapplied, especially when employed as a synonym for the entire island of intrachondrial bone, whereas it was originally applied only to the specific ossification sites within the cartilage lacunae.

It should be stressed that the intrachondrial islands of bone are a normal feature of the middle layer of the otic capsule and are found in species other than man. They have also been described as prominent persisting histologic features in certain pathologic processes of bone characterized by aberration of the developmental pattern, such as fetal chondrodystrophy, osteogenesis imperfecta (osteopetrosis), osteomalacia and rickets. There has been a plethora of literary effort expended in an attempt to elucidate the process whereby calcified cartilage islands undergo transformation into endochondral bone. It has generally been considered a process of metaplasia. Dissenting opinions have been expressed, however, and notably by Bast. This investigator observed the invasion of cartilage lacunae by undifferentiated mesenchymal cells of the osteogenetic buds, which were responsible for the evacuation of cartilage cells debris and the assumption of osteoblastic function. Thus is explained the multitude of cells frequently seen within the lacunae of chondrocytes in the cartilage islands, and it bears comparison with the characteristic solitary cell found in the typical cartilaginous lacuna. The subsequent course of definitive ossification provides the unusual histologic features which make the term "intrachondrial" so appropriately descriptive of this modified type of bony tissue.

In the process of ossification of the cartilaginous capsule, the first center of ossification appears in the 126-mm. (16½-week) fetus, the last, or fourteenth, in the 183-mm. (21-week) fetus. The maximum size of cochlea, canals and of surrounding capsule is attained at the time their ossification centers appear. Each center is, except for its peripheral shell of periosteal bone, composed of intrachondrial bone.

Unlike the periosteal layer, which is very active early in the ossification process and relatively quiescent in the latter part of fetal life, formation of the endochondral (replacement) bone around the islands of intrachondrial bone progresses slowly (except around the canals) until the 39th week (near term). Immediately after birth the marrow of the middle and outer layers is rapidly replaced by bone, so that by the third year all the layers consist of compact bone, and the lines which once sharply separated them are virtually obliterated.

Endochondral bone is formed in the same way that perichondrial bone is produced; however, it is laid down around the islands of intrachondrial bone and in spaces which were filled with cartilage previous to their excavation by osteogenetic buds. This new bone,

which fills the excavated spaces, is a primary endochondral bone; normally it remains as such throughout life. In other bones of the body primary bone of similar nature is usually removed, to be replaced by secondary, or haversian, bone if it is replaced at all. In the otic capsule, on the contrary, it persists; after it is fully formed, the capsule itself undergoes no further expansive growth.

The first center of ossification appears in the fetus of 16 weeks (120 mm.), the fourteenth, or last, in the fetus of 21 weeks (183 mm.). Ossification of the capsule is thus completed in a period of five or six weeks, at midterm.

In the fetus of 126 mm. (16 weeks), four centers are present in the following positions: Center 1, under the first turn of the cochlea, in front of cochlear (round) window; Center 2, under the ampulla of the posterior canal; Center 3, over the nerves to the ampullae of the superior and lateral canals; Center 4, above the vestibular (oval) window.

In the fetus of 147 mm. (18 weeks) the remaining centers, with the exception of the last, are present: Center 5 arches over the internal acoustic meatus; Center 6 lies over the cochlear nerves; Center 7, on the upper wall of the internal acoustic meatus, becomes continuous with Center 5 to complete an arch over the meatus; Center 8 lies above the cochlea; Center 9 is located on the inferior aspect of the meatus; Center 10 develops near the common crus of the superior and posterior canals; Centers 11, 12, 13 form near the vestibular window and are superiorly placed between the vestibule and the cochlea.

In the 183-mm. (21-week) fetus, Center 14 has appeared over the crus of the posterior canal.

In the fetus of 155 mm. (19 weeks) all centers except Center 14 have fused with one or more centers to form one continuous bone.

Peripherally, each ossification center is composed of periosteal bone; on deeper level the center is made up, at first, of the cartilage islands. In this remarkable tissue cartilage never wholly disappears. The manner in which the intrachondrial bone is formed and the degree to which it remains a primitive tissue now calls for review.

In the 147-mm. (18-week) fetus the cartilage cells are enlarging and the chondral matrix between them is undergoing calcification (Fig. 1a).<sup>\*</sup> At other sites, in the same capsule, the change

<sup>\*</sup>This and the descriptions of the succeeding seven stages are based in part upon the earlier account by Bast.<sup>16</sup>

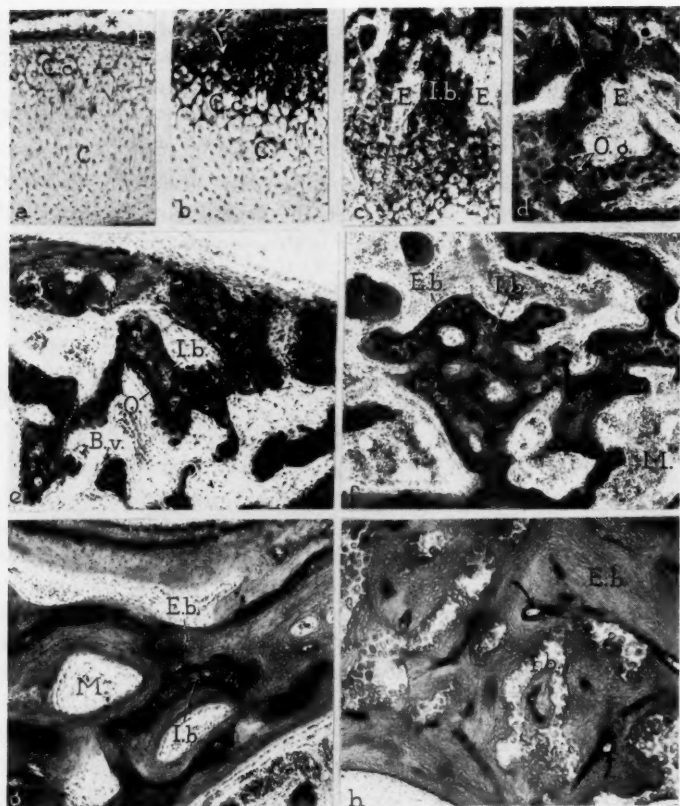


Fig. 1.—Photomicrographs of sections showing successive steps in the formation of bone in the middle, or endochondral, layer of the otic capsule. X 59. *a*, 147-mm. fetus, at the site of ossification center No. 10 (Wis. ser. 38, sl. 23, sect. 8); *b*, same specimen (sect. 3); *c*, 150-mm. fetus (Wis. ser. 39, sl. 26, sect. 8); *d*, 161-mm. fetus (Wis. ser. 13, sl. 36, sect. 5); *e*, 183-mm. fetus (Wis. ser. 21, sl. 49, sect. 5); *f*, 230-mm. fetus (Wis. ser. 2, sl. 51, sect. 3); *g*, same specimen (sl. 56, sect. 5); *h*, adult of 19 years (Wis. ser. 29, sect. 339).

Abbreviations in Figs. 1, 4 and 5: *B.v.*, blood-vessel; *C*, cartilage; *C.c.*, calcified cartilage; *Co.*, cochlea; *C.t.*, connective tissue cells; *D.*, dura mater; *E.*, excavation (in cartilage); *E.b.*, endochondral bone; *I.b.*, intra-chondrial bone; *M*, marrow; *O.*, osteoblasts; *O.g.*, osseous globules (*globuli ossei*); *P.*, perichondrium; *S.c.*, semicircular canal. Numerals indicate layers: 1, periosteal; 2, endochondral; 3, endosteal. In Fig. 1*a*, \* indicates a tear in the perichondrium; in Fig. 1*b*, the arrow marks the site of invasion by bone-forming cells; in Fig. 1*b*, the arrows point to canals containing blood vessels.



in the cartilage is somewhat more advanced; osteogenetic cells (Fig. 1*b*, top; Fig. 1*c*, bottom)\* from the periosteum enter the lacunae of the calcified cartilage of the developing ossification center, replacing the cartilage cells of each but leaving the matrix. After considerable areas have thus been changed, the vascular osteogenic buds enter and excavate areas within this changed cartilage (Fig. 1*c*, top, at E). In the 150-mm. (18½-week) fetus the unexcavated areas of this altered cartilage (Fig. 1*c*, at I.B.) gradually become ossified by the deposition of bone around the individual osteoblastic cells which have wandered into the lacunae. These nests of bone, globular in form and filling each lacuna, are the so-called "globuli ossei" of Brandt (see footnote on page 605). These globules together with the surrounding calcified cartilaginous matrix, will be referred to hereinafter as intrachondrial bone (Figs. 1*d* to 1*b*, at I.B.). In portions of the capsule of the 161-mm. (19-week) fetus virtual filling of the lacunae has been accomplished (Fig. 1*d*). With this formation of globular masses of true bone (globuli ossei) within the calcified cartilage matrix, definitive intrachondrial bone is established. Now, in the excavated areas (Fig. 1*d*, at E) the young connective tissue is becoming differentiated into a pre-osseous tissue. In the 183-mm. (21-week) specimen the cells of the pre-osseous tissue of the preceding stage, bordering the islands of intrachondrial bone, become enlarged; they are beginning to deposit endochondral bone (Fig. 1*e*). From this time onward, the change is one of further formation of endochondral bone; intrachondrial bone undergoes no further notable change. At the 230-mm. stage (fetus of 26 weeks) endochondral bone is forming an investment for the intrachondrial bone (Fig. 1*f* and 1*g*). The endochondral formation is slow in the cochlear region to the time of birth; in other regions (for example, the canalicular) its development is rapid and may be complete at birth. Marrow cells are forming within the tissue of the excavated areas (Fig. 4, at M.). In the adult temporal bone the intrachondrial bone persists as a striking constituent of the middle layer of the osseous otic capsule (Fig. 1*b*; compare Fig. 19 in Bast<sup>16</sup>). Its relatively abundant presence distinguishes the otic capsule histologically from other bones in the human skeleton. Remarkably, its texture in the adult temporal bone (Fig. 1*b*) differs but slightly from that in the fetus of the seventh month (Fig. 1*f*); the intrachondrial bone seems to retain the quiescence which characterizes ordinary, unmodified, cartilage. In point of fact, in some

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\*In the lower part of Fig. 1*c* the process is similar to that in the upper part of Fig. 1*b*. The excavated areas of Fig. 1*c* become obliterated by production of endochondral bone (see Figs. 1*g* and 1*b*).

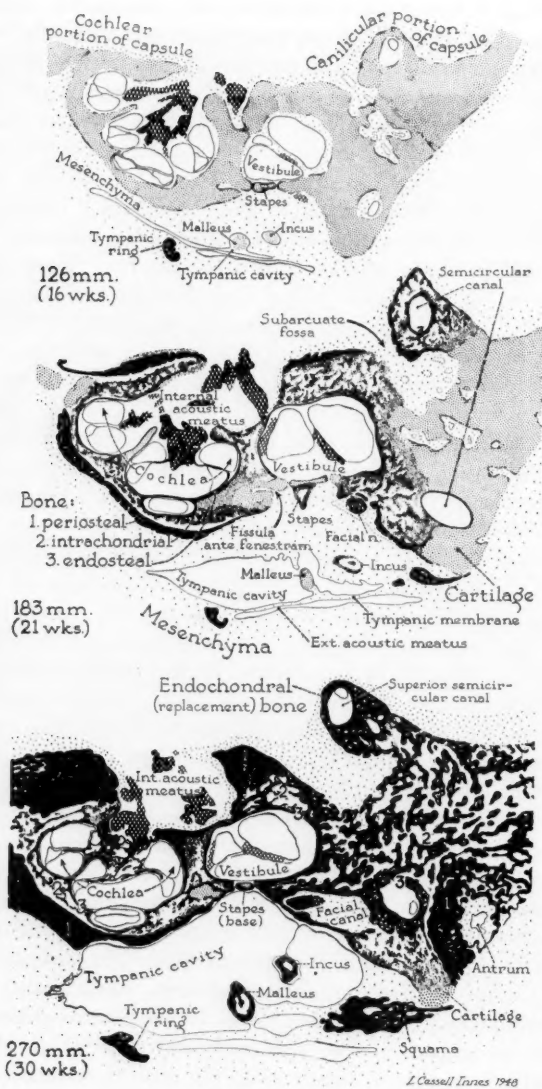


Fig. 2—Drawings of sections of the cartilaginous otic capsule and auditory ossicle and of the temporal bone, depicting crucial steps in development. Semidiagrammatic, from Edinger tracings. X 4 1/16. *a*, 126-mm. (16-week) fetus (Wis. ser. 11, sl. 27, sect. 5); *b*, 183-mm. (21-week) fetus (Wis. ser. 21, sl. 40, sect. 2); *c*, 270-mm (30-week) fetus (Wis. ser. 107, sl. 26, sect. 8).

parts of the intrachondrial bone true cartilage cells may persist throughout life, due to failure of the osteoblasts to wholly dispose them. Like cartilage, too, it is relatively avascular, a circumstance dependent upon a mechanism of formation through the operation of which the invasive bone cells tend to seal themselves off from the surrounding tissue.

In order to demonstrate the progress of ossification in the otic capsule, reference to five stages will be adequate (16, 21, 30 and 40 weeks, and the adult of 65 years). It will become evident that, whereas the three types of bone develop at different rates, maturity is attained by all of them in the fetal stage.

In the 126-mm. (16½-week) fetus the capsule is still largely cartilaginous (Fig. 2*a*).<sup>\*</sup> In the course of subsequent growth its general configuration remains similar; in fact, the capsule itself undergoes no dramatic change in form even when it has become imbedded in a thick periosteal shell.

In the 183-mm. (21-week) fetus cartilage is present at the posterior portion of the canalicular capsule, around the fissula and on the base of the stapes (Fig. 2*b*). Endosteal bone forms a complete shell for the labyrinthine spaces (cochlea, vestibule, canals); no further growth takes place since no epiphyseal areas exist. Periosteal bone is now in a state of active formation; its location is peripheral as it constitutes part of the cranial and tympanic walls. Intrachondrial bone occurs between the periosteal and endosteal layers; its presence lends a spongy appearance to the entire capsule. Growth of the capsule having ceased, the continuing deposition of periosteal bone will serve to imbed the otic capsule in the petrous portion of the temporal bone of the adult cranium.

At 270 mm. (30 weeks), cartilage persists on the vestibular and articular surfaces of the stapes, in the fissular region and at the area of union with the squama (Fig. 2*c*). Periosteal bone is a thickening stratum, its expansion serving, for example, to deepen the internal acoustic meatus (Fig. 2*c*, upper part of section). It gradually spreads to invade the lateral, or antral, part of the capsule. Endochondral bone now develops rapidly in the capsule in the region of the semicircular canals. It begins to invest the "spicules" of changed cartilage which were sequestered during initial stages in ossification of the primordial capsule. Periosteal bone, so recently formed in the antral region, has begun to undergo local destruction;

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<sup>\*</sup>Completely chondral at the level illustrated (Fig. 2*a*); in other sections early ossification is evident.

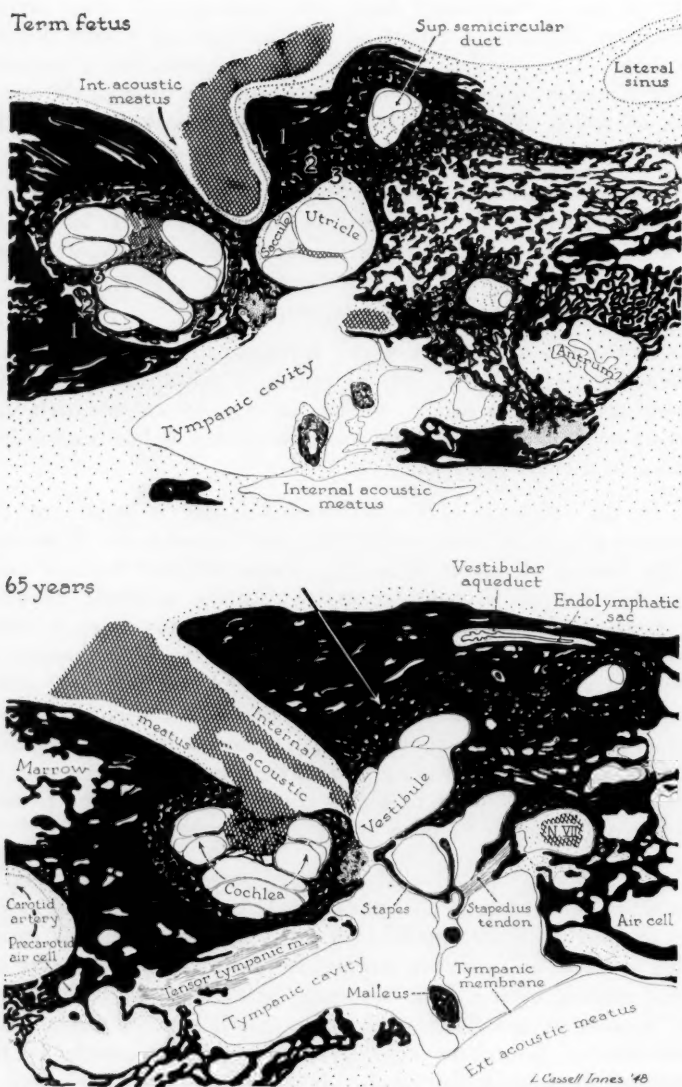


Fig. 3.—Drawings of sections of the temporal bone and auditory ossicles, continuing and concluding the crucial steps in development. Semi-diagrammatic, from Edinger tracings.  $\times 4 \frac{1}{3}$ . *a*, term fetus (Wis. ser. 95, sl. 51, sect. 3); *b*, adult of 65 years (Wis. ser. 1, sl. 31, sect. 185). In *b*, the arrows through the outer layer of bone pass to the line of the latter's continuity with the middle layer.

the mucous membrane is already replacing this layer of osseous tissue and the associated marrow (Fig. 2c, lower right).

It is important to emphasize the statement that endochondral bone around the canals develops rapidly once the ossification centers have appeared. Previously (for example, in the 183-mm. fetus) intrachondrial and periosteal bone were the only types present. In the 270-mm. fetus the endochondral bone, in the area of primary appearance, has completely filled the excavated areas around the intrachondrial islands. The capsule then becomes locally solid and deserves the term "petrous." In the cochlear division of the capsule endochondral bone does not begin actively to close comparable spaces until the fetus has reached the stage of term. In some specimens this change occurs even later. This is equivalent to saying that during approximately a ten-week period, ending with term, endochondral bone formation progresses rapidly in the canalicular part of the capsule, and then is shifted to the cochlear region, the waves of osteogenesis being successive rather than concurrent.

In the term fetus the periosteal layer is thick in the cochlear region (Fig. 3a). Intrachondrial bone in the same region is reduced in relative amount through deposition of "replacement" (endochondral) bone upon the spicules of intrachondrial bone. Marrow spaces between the periosteal and the endosteal bone have been reduced in size and number, forecasting ultimate fusion of these two osseous strata.

In an adult of 65 years periosteal and "replacement" bone together make up almost the total bulk of the capsule and of the bone deposited thereon (Fig. 3b). The replacement bone is a combination of the intrachondrial and endochondral types; the former (intrachondrial) forms the "skeleton" upon which the latter (endochondral) has been deposited. In the adult the intrachondrial bone persists unchanged; the endochondral bone has almost completely obliterated the marrow spaces.

As has been demonstrated by the use of reconstructions, ossification takes place through the activity of osteogenic tissue in a total of 14 centers; the first of these appears in the 120-mm. (16-week) fetus, the last in the fetus of 183 mm. (21 weeks). Fusion of all centers but the last is completed in the 155-mm. (19-week) fetus, to enclose the cochlea and the semicircular canals (Bast,<sup>10</sup> Figs. 30 to 42).

In four selected specimens the major steps in ossification may be traced again, employing photomicrographs of the canalicular and cochlear walls.

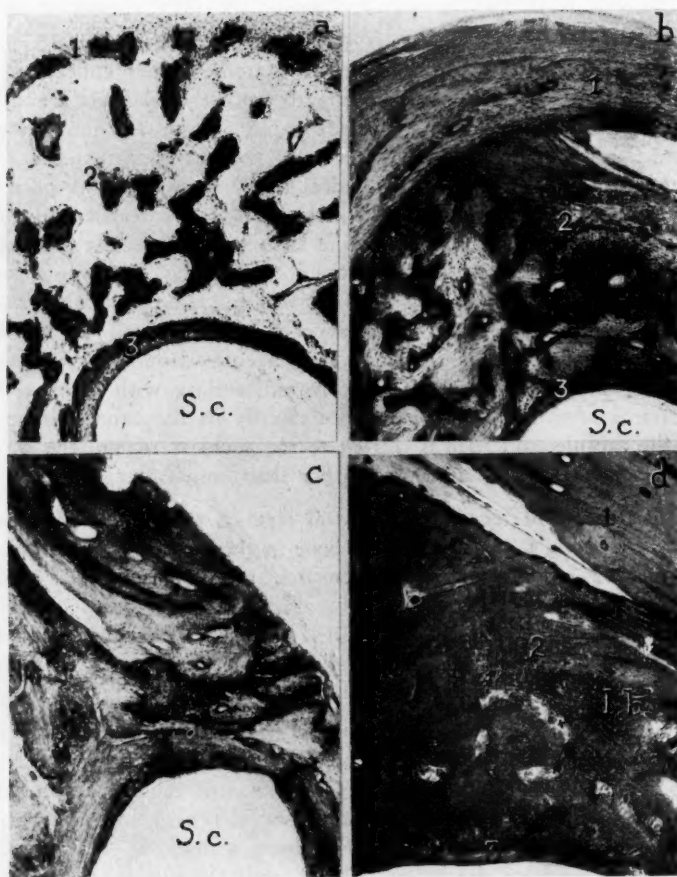


Fig. 4.—Photomicrographs of sections through the canalicular part of the capsule showing stages in ossification. X 35. *a*, 183-mm. fetus (Wis. ser. 21, sl. 49, sect. 3); *b*, 270-mm. fetus (Wis. ser. 107, sl. 26, sect. 10); *c*, term fetus (Wis. ser. 95, sl. 51, sect. 3); *d*, adult of 65 years (Wis. ser. 1, sect. 185).



The canalicular capsule of the 183-mm. fetus consists of a thin inner (endosteal) layer and a highly spongy, but relatively thick, middle layer which still consists wholly of intrachondrial bone (Fig. 4*a*). By the 270-mm. stage considerable advance has been made. In the middle layer endochondral bone has been deposited heavily upon the intrachondrial bone to produce an almost solid stratum (Fig. 4*b*); the latter has fused with the still thin inner (endosteal) layer and the now thick outer (periosteal) layer. Despite the fact that each has assumed definitive appearance, their boundaries are readily discernible. In the 65-year adult solidity is a more striking feature (Fig. 4*d*); the boundary line between the outer and the middle layers is distinguishable, but that between the latter and the inner layer is not.

In the cochlear portion of the otic capsule ossification at first progresses rapidly, then is soon outstripped by the canalicular part. In the cochlear wall of the 183-mm. fetus, in addition to the inner and middle layers, the outer layer is well developed (Fig. 5*a*). In the 270-mm. fetus only the outer layer displays appreciable advancement (Fig. 5*b*); the inner layer remains thin, and the middle layer is represented by intrachondrial bone only, lodged in marrow.\* At term the formation of endochondral layer has progressed to a point at which all intrachondrial tissue is invested by endochondral bone (Fig. 5*c*). Marrow spaces, now smaller, are still numerous. The presence of the intrachondrial islands, with but little endochondral bone surrounding them, and the occurrence of marrow spaces render this layer, in the cochlear region at this stage, easily distinguishable from the periosteal bone, in which small canals take the place of marrow spaces.

Even in the adult of advanced age (65 years) these two layers retain distinctive features (Fig. 5*d*); in the middle layer the intrachondrial bone maintains its striking histological character, despite the fact that the marrow spaces have been almost completely obliterated by the formation of endochondral bone.

The excessively dense, or stony, nature of the otic capsule is largely due to the compactness of the middle layer. Density is not a characteristic of the apical, antral, and mastoid portions, which develop relatively late in the process of ossification. These regions

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\*Intrachondrial bone is usually more abundant than it is in this particular specimen. Its regular distribution is recorded in the other three figures (Figs. 5*a*, 5*c* and 5*d*).



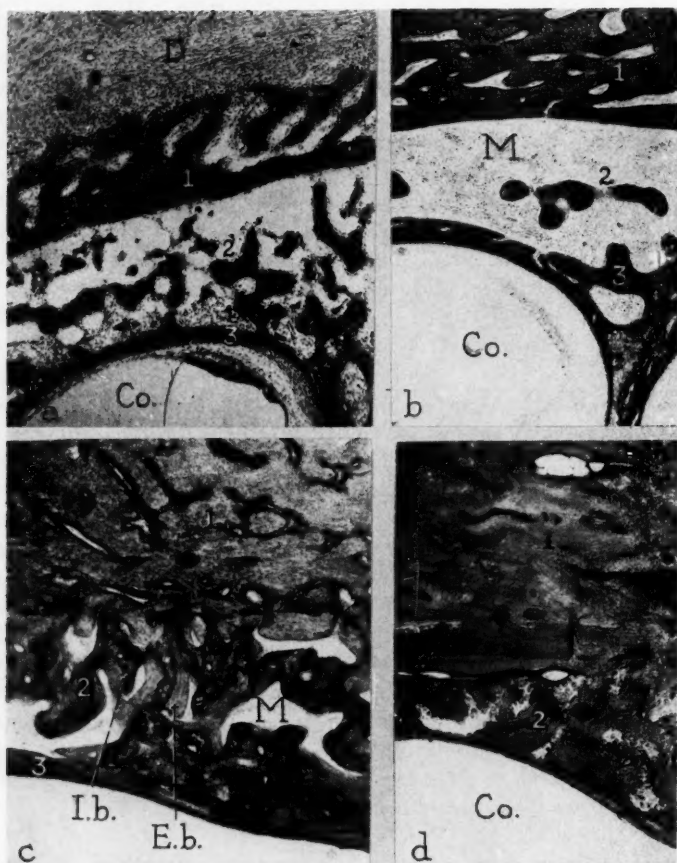


Fig. 5.—Photomicrographs of sections through the cochlear capsule showing stages in development of the perichondral and intrachondrial bone. X 35. *a*, 183-mm. fetus (Wis. ser. 21, sl. 49, sect. 3); *b*, 270-mm. fetus (Wis. ser. 107, sl. 26, sect. 2); *c*, term fetus (Wis. ser. 95, sl. 51, sect. 3); *d*, adult of 65 years (Wis. ser. 1, sect. 185).

might properly be regarded as extracapsular. The extracapsular part (composed of a late fetal and early extension of the outer capsular layer) is not likely to be petrous, but is actually pneumatic. The air cells, whose presence accounts for the cavernous nature of the bone, spread from the auditory tube and the tympanic cavity into the periosteal layer, and, in certain restricted areas, into endochondral bone.

Pneumatization of the tympanic cavity (middle ear), produced by the invasion of the nasopharyngeal epithelium through the auditory tube into the connective tissue of the embryonic middle ear, begins in the 25-mm. (8-week) embryo, when the capsule is precartilaginous. At first its advance is slow, the condition being similar in the 50-mm. (11-week) fetus, at which stage the capsule is formed in cartilage. In the 260-mm. (29-week) fetus, the tympanic epithelium has reached the mouth of the developing antrum (see 270-mm. fetus, Fig. 2c).

Cells spread from the tympanic cavity or from the auditory tube. They appear as epithelial buds in a fetus of 246 mm. (27½ weeks). Cells of the precochlear group (lateral to the lateral canal, between the auditory tube and the apex of the cochlea) are present in a 235-mm. (26-week) fetus; postcarotid cells (medial and posterior to the carotid canal and medial to the cochlea) appear in a 345-mm. (37-week) fetus and may extend anteriorly to become apical in position; precarotid cells (between the canal and the auditory tube) are inconstant. Cells of the supracochlear group (lying above the cochlea, anterior to and above the geniculate ganglion) are sometimes extensions of the precochlear cells. Most of the air cells are formed in young bone before marrow is produced. Where marrow is already present (as it is in the areas of the future antral, postcarotid and some of the supracochlear cells), the epithelium does not invade the marrow directly; rather, it extends into diploic bone, the marrow becoming less dense and cellular prior to invasion, and recedes in front of the advancing mucous membrane.

The progress of pneumatization is rapid; in young children the process may be complete.\* The degree to which air-cells replace bone is astonishing. This is particularly so in a specimen from a child 13 years of age, in which the air cells not only occupy the antral and apical areas but also form continuous arches of cells under the internal acoustic meatus (Figs. 6a and 6b) and the coch-

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\*In a specimen of a child of four and a half years, pneumatization was obviously mature and stable (Anson, Wilson and Gaardsmoe<sup>14</sup> Figs. 10-19).

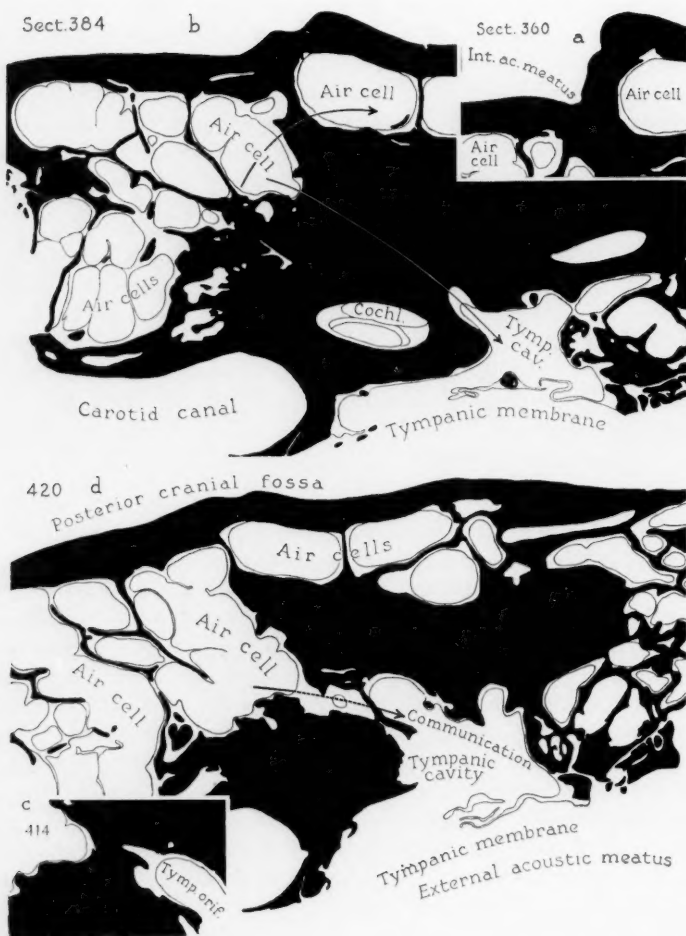


Fig. 6.—Drawings of sections of the temporal bone of a child 13 years of age (Northw. ser. 3.8.'35) showing the air cells. Semidiagrammatic. X 31. In *b*, the upper arrow indicates the direction of communicating cells (in adjacent sections) under the internal acoustic meatus; the lower arrow records the course of similar communications under the cochlea. Section 360 (Fig. 6*a*) passes through the cranial orifice of the internal acoustic meatus at the latter's inferior limit. Section 384 (Fig. 6*b*) passes through the lowermost portion of the cochlea. Sections 414 and 420 (Figs. 6*c* and 6*d*) are situated inferior to the horizontal level of the cochlea and the canals. The arrow in *d* follows the course of a broad communication (complete in succeeding sections) between the tympanic cavity and the air cells which extend medialward to the diploic wall of the cranial cavity.

lea (Figs. 6c and 6d).<sup>\*</sup> At a horizontal level caudal to the cochlea, the cells occupy all of the bone from the wall of the cranial fossa medially to that of the tympanic cavity laterally—with a capacious outlet into the latter (Fig. 6c). In this specimen, despite extensive replacement of periosteal bone, the endochondral layer (of the otic capsule) remains substantially intact. That is to say, although surrounding bone of the so-called petrous portion undergoes profound fetal and postnatal remodelling, the capsular house of the sensory organs remains relatively impregnable.

Reviewing briefly the special features which mark as striking the developmental history of the otic capsule, it is a fact of primary importance that the centers of ossification, numerous and circumferential, fuse to form a box-like covering for the labyrinthine structures between whose elements no areas persist to allow for subsequent expansion. Contact between neighboring centers is completed in the midterm fetus. Thereupon, growth ceases in the capsule. This means that the temporal bone of the adult is larger than its predecessor in the fetus, not because of capsular expansion, but because new periosteal layers are applied to its exterior, to embed the capsule ultimately in a mass whose dimensions are much greater than its own. Equally striking is the fact that no sooner has replacement bone begun to appear prominently in the capsule than there is initiated a phase of concurrent erosion of the periosteal layer; mucous membrane, spreading from the tympanic cavity, renders the temporal bone pneumatic. Its petrous portion is, in many specimens, its lesser part.

#### AUDITORY OSSICLES

In presenting the descriptions of the auditory ossicles, special attention will be given to the developmental anatomy of the stapes, because of its intimate relation to the otic capsule. For the malleus and incus briefer account must suffice.<sup>\*\*</sup>

In the embryo (for example, one of 28 mm.)<sup>\*\*\*</sup> the primordia of the auditory ossicles are branchial in location; the primitive malleus

<sup>\*</sup>It should be added that these two examples are described in order to record the degree to which pneumatization may alter the internal structure of the temporal bone, and the speed with which the process sometimes progresses. In many specimens in the authors' collections distribution of the air cells is far less extensive. A detailed report is in preparation by the senior author and associates.

<sup>\*\*</sup>The reader is referred to companion articles which describe and figure major steps in the morphogenesis of the three ossicles.<sup>2, 3</sup>

<sup>\*\*\*</sup>As will be understood, length does not increase by consistent steps with advancing fetal age, nor are records of age always dependable; evident inconsistencies in relation of length to age could be due to either or both of these factors.

is continuous with the first branchial arch, the incus is near the second; the stapes, seemingly, has acquired independence. They grow only through the first half of intra-uterine life and to only five times the primordial dimensions. When these branchial structures are still cartilaginous, the mandible has begun to form in membrane bone. It will ultimately envelop Meckel's cartilage, and the latter will be resorbed.

In the fetus of 111 mm. the malleus is broadly continuous with Meckel's cartilage, but the stapes is separate from Reichert's cartilage. In the malleus rarefaction of the cartilage is evidenced, a histological change which precedes the formation of bone. The incus and the stapes are as yet unaltered.

Ossification occurs first in the incus (at 117 mm.), next in the malleus (at 126 mm.), last in the stapes (at 146 mm.). The centers for malleus and incus are established in the 135-mm. fetus on the long crus of the incus and on the ventral aspect of the malleus at its junction with Meckel's cartilage.

In the fetus of 146 mm., ossification begins on the obturator aspect of the crus and of the base of the stapes. At the same time, ossification is well advanced in the long crus of the incus and has not affected the short crus. Perichondrial bone covers both ossicles at the site of the articulation. For each ossicle there is a single center of ossification.

At the 222-mm. stage, Meckel's cartilage is a lancet-shaped bar; it is still continuous with the malleus. In the malleus, endochondral bone is forming. The stapes is not only deeply excavated, but its obturator wall (capital, crural, basal) has been partially removed by osteoclasts. The original marrow cavity is exposed to the invading mucous membrane. Endochondral bone spreads across the cartilage of the base. Later the original perichondrial bone will be almost entirely removed; the newly formed endochondral bone is permanent.

By the 345 mm. stage, endochondral bone formation in the malleus and incus has progressed to the point where they exhibit relative solidity. The stapes, on the contrary, has been reduced to the state of a morphologic wraith. It is thin throughout; the obturator, or inner, wall has been sacrificed. Marrow has disappeared. Mucous membrane occupies the former site of marrow tissue.

Now to consider in greater detail the special features which characterize the development of the stapes, first employing reconstructions, then semidiagrammatic drawings of sections.

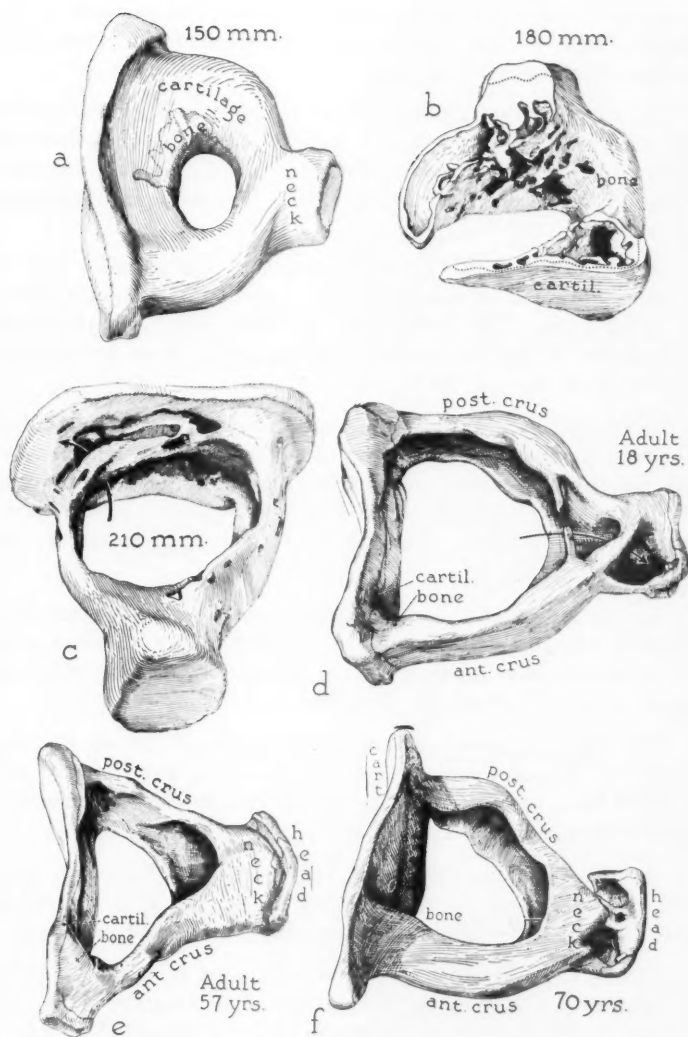


Fig. 7.—Reconstructions of stapes, from three fetal and three adult specimens, showing stages in development and variation in adult form. X 17. *a*, 150-mm. fetus (Wis. ser. 39); *b*, 180-mm. fetus (Wis. ser. 45B); *c*, 210-mm. fetus (Wis. ser. 51); *d*, adult of 18 years (Northw. ser. 2.26.'30); *e*, adult of 57 years (Northw. ser. 1.14.'33); *f*, adult of 70 years (Northw. ser. 3.3.'34). In *b* an upper portion has been removed to reveal the extent of hollowing; in *c* an arrow passes beneath the stapedial crest; in *e*, through an opening in the eroded head. Dotted lines indicate the extent of cartilage and bone.

In the 50-mm. (10-week) fetus the definitive portions of the stapes are clearly recognizable; at an earlier stage, 25 mm. (8 weeks), the stapes is still virtually a ring.

The stapes of the 126-mm (16½-week) fetus is a cartilaginous element of true stirrup form. A cylindrical head and a flattened base join equally robust crura. The intercrural space, or obturator foramen, is relatively small and circular. The tissue is unmodified cartilage.

In the 150-mm. (18½-week) specimen the posterior crus is the more bulky and bowed of the pair, forecasting a regular difference in the adult. The single center of ossification has appeared on the obturator surface of the base (see Fig. 7*a*). Bone spreads rapidly therefrom, toward the head.

In the 160-mm. (19½-week) fetus, ossification involves all of the base except the vestibular aspect, which always remains cartilaginous. At the capital end bone has not yet crossed the obturator wall. While bone spreads to produce a complete ring, it is being destroyed on the inner (obturator) surface, left intact on the outer aspect.

At the 180-mm. (21-week) stage, bone has spread to surround the entire obturator foramen. Crura and base are hollowed (Fig. 7*b*). Concurrently with continuing ossification, the newly-formed bone is removed around the obturator wall.

The entire obturator surface, in the 210-mm. (23-week) fetus, has been destroyed by osteoclasia. In the base, some of the perichondrial bone persists as a marginal lip and, in some specimens, as the transverse stapedial crest (Fig. 7*c*).

At the 245-mm. (27-week) stage, adult configuration is almost attained and is actually reached in the 275-mm. (30-week) fetus. In all specimens cartilage remains on the head and base.

In the term fetus (Fig. 7*d*), infant, child or adult (Fig. 7*e*), the head of the stapes may be perforated or uneroded (Fig. 7*f*); the margin of the base may be prominently lipped (Fig. 7*d*) or flattened (Fig. 7*e*), the crura bowed (Fig. 7*e*) or relatively straight (Fig. 7*f*).

Reviewing certain of these developmental features with the aid of illustrative sections, it may be pointed out that in one specimen of 167 mm. (20 weeks) the stapes is still entirely cartilaginous, although ossification has been initiated in the otic capsule (Figs. 8*a* and 8*b*).



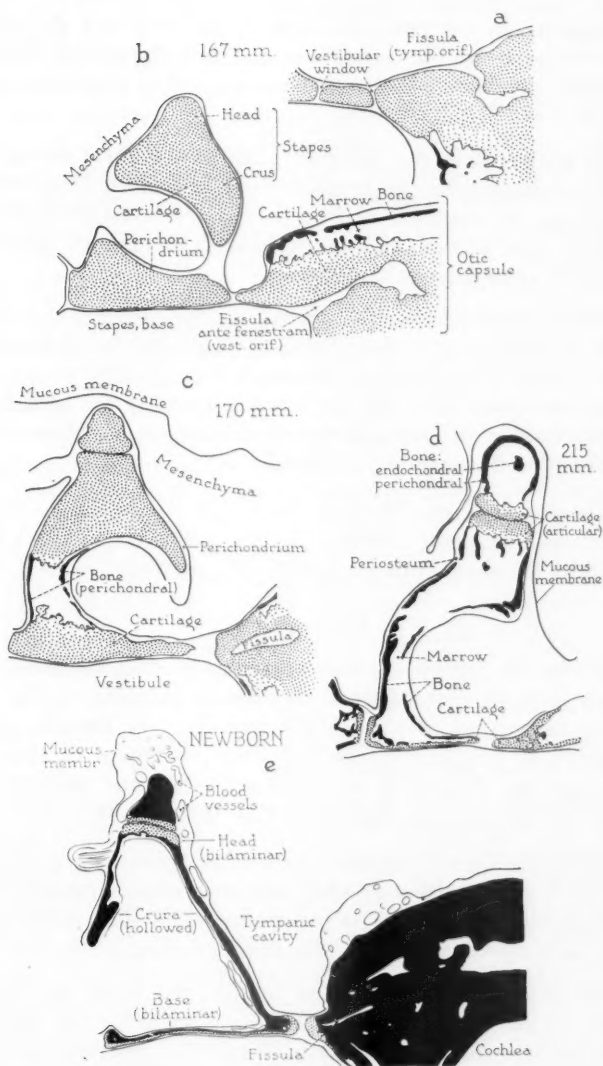


Fig. 8.—Drawings of sections of stapes showing four steps in development. Semidiagrammatic, from Edinger tracings. X 12. *a*, 167-mm. (20-week) fetus (Wis. ser. 105, sl. 23, sect. 8); *b*, 167-mm. fetus (Wis. ser. 105, sl. 19, sect. 9); *c*, 170-mm. (20-week) fetus (Wis. ser. 131, sl. 20, sect. 8); *d*, 215-mm. (24-week) fetus (Wis. ser. 62, sl. 28, sect. 4); *e*, newborn (Wis. ser. 315, sl. 20, sect. 8).

At approximately the same age in other specimens periosteal bone appears on the obturator wall of the base and the adjacent basal extremities of the crura, that is, internally on the surface of the ossicle. However, it does not yet succeed in producing a complete periosteal shell.

As is evident in the 170-mm. stage (20 weeks), the periosteal plate is rendered perforate as rapidly as it is formed (Fig. 8c). On the opposite, or external, surface, however, the layer remains undisturbed. Intrachondrial bone is formed to minimal degree and is removed as rapidly as it is formed.

After conversion of the crura into hollow columns, gradual erosion of cartilage extends to the base, finally to the neck and head of the stapes. This has been accomplished in the 215-mm. (24-week) fetus (Fig. 8d). By the time the cartilage has been reduced to a thin lamella on basal and capital extremities, the obturator wall has been almost completely removed.

The stapes of the 290-mm. fetus (32 weeks) is, in all major features, a fully mature ossicle. In the newborn (Fig. 8e) and in the adult, the stapes remains essentially unchanged.

#### CONCLUSIONS

In the otic capsule the first of a total of 14 ossification centers appears early in the fourth lunar month (16 weeks, 120 mm.). Centers have fused to form a complete box, or capsule, prior to the middle of intra-uterine life (19 weeks, 155 mm.). Thus, adult dimensions are attained at approximately the same time the stapes attains full size—in the short period of three weeks.

Although the otic capsule of the midterm fetus is as large as it will ever be, it is neither histologically mature nor embedded in the extracapsular osseous tissue whose outline lends the typical form to the so-called petrous part of the temporal bone.

Of the three layers of the capsule the inner, or endosteal, stratum is the simplest; it forms a mere shell for the labyrinthine canals, cochlea and vestibule; it is complete at midterm and undergoes no further increase in size.

The outer, periosteal layer appears in the cochlear region of the capsule during the eighteenth week (147 mm.), and is complete before the eighth month (27½ weeks, 246 mm.). In the canalicular part of the capsule it appears later (21 weeks, 183 mm.); it spreads beyond the limits of the original capsule, toward the mas-

toid region; it continues to expand, as an extracapsular addition, until puberty.

Of the three layers the middle (intrachondrial and endochondral tissues combined) is the most complex in structure. In both cochlear and canalicular divisions of the capsule intrachondrial bone appears in the fetus of  $4\frac{1}{2}$  months (18 weeks, 147 mm.); these cartilage islands attain maximum distribution within a period of about six weeks after primary appearance (that is, at 24 weeks, or in the 215-mm. fetus). Around the cochlea they retain fundamental form for almost a month (up to the stage of  $27\frac{1}{2}$  weeks, or 246 mm.). Thereupon slow formation of endochondral bone is initiated, the cartilage islands becoming covered by a thin layer of the endochondral bone—without other alteration of the "spicules" upon which deposition of the replacement bone takes place. At term the process is suddenly accelerated, continuing through the first of infancy with such alacrity that the cochlear region comes suddenly to resemble closely that of an adult bone. In the region of the canals there is no such initial lag in development. From the first (beginning as in the case of the cochlea) the deposition of endochondral bone around the canals is rapid up to the stage of 7 or 8 months (30 weeks or 270 mm.), after which stage it is slow. Activity begins in the region of the superior semicircular canal; posterior and lateral canals follow; the intervening tissue is the last to be formed in endochondral bone.

The intercanalicular area (the portion surrounding the compact capsule of the canals) never becomes converted into bone of fully petrous character. It retains marrow spaces, which may persist in the adult ear or be replaced—beginning in the seventh month ( $27\frac{1}{2}$ -weeks, or 246-mm. stage)—by pneumatic spaces which spread from the tympanic antrum. When such occur, invasion by the mucous membrane may progress so rapidly as to be complete (that is, of "adult" distribution) in the young child (three years old). Except for this portion of the capsule, pneumatization is restricted to bone of periosteal nature which was added peripherally to the primordial osseous capsule. In other words, except in the territory named, the process of mucosal invasion leaves untouched the capsule as it existed in the fetus at midterm.

Altogether, then, the development of the otic capsule is one of rapid progress, resulting in astonishingly early formation of an osseous encapsulating "box" for the organs of hearing and equilibrium. Growth is precluded by the fusion of the numerous centers of ossification, between which there occur no zones for epiphyseal

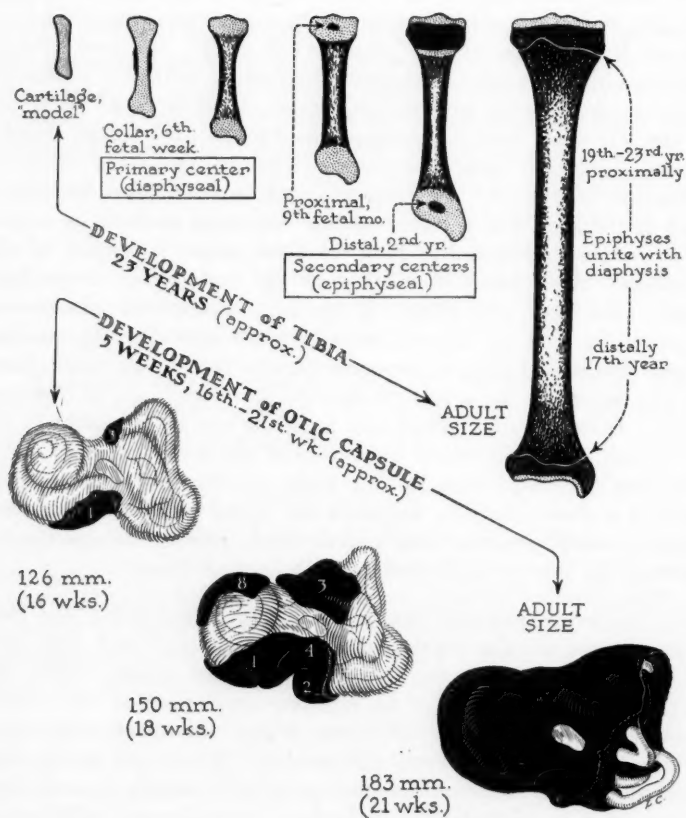


Fig. 9.—Comparative development of the otic capsule and the tibia. Diagrammatic. A portion of the capsule removed in the reconstruction of the 183-mm. to expose the semicircular ducts. Ossification centers numbered in accordance with the scheme of Bast.<sup>16</sup>

expansion. In the "spaces" between periosteal and endosteal layers, where marrow might be expected to occur, such tissue is usually replaced by bone of endochondral character, a fact which renders the capsule relatively solid, or petrous. Such tissue is not removed, as it would be in a typical long bone, to make way for marrow. When removed, the change occurs to permit spread of mucous membrane, from tympanic cavity or auditory tube. Concurrently, periosteal bone, added to the capsule in the latter half of fetal life, is similarly invaded to form the cells of the apical and related portions of the temporal bone.

In the stapes the single ossification center appears soon after the fetus passes the fourth lunar month. The ossicle attains full (adult) dimensions about the middle of intra-uterine life (before the 21st week, or 183-mm. stage); it possesses adult form before birth (at or before the 32nd week, that is, before the eighth lunar month or 290-mm. stage). Endochondral bone persists only in the internal aspect of the head and base; in each of these areas it appears as a thin plate lining an "articular" cartilage. The stapes forms without epiphyseal areas of growth, and therefore does not increase in size after bone becomes continuous around the obturator wall. During ossification it becomes hollowed at the capital and basal extremities, and channelled throughout the entire length of each crus. Marrow, the while, retreats before the advance of the tympanic mucous membrane. Concurrently the stapes loses more than one half of its maximal bulk, being robust in early fetal life, fragile later.

In order to emphasize the degree to which the capsule and the stapes depart from the standard pattern of development, it is essential to keep in mind the steps in morphogenesis of a typical long bone. A human tibia will serve as an example.

The cartilage "model" of a tibia suggests, in a general way, the form of the future bone (Fig. 9, upper line of stages). A shaft or diaphysis, ends in slightly enlarged extremities, which are the future epiphyseal areas (Fig. 9, 1st stage). Ossification begins in the diaphysis, in a primary center to produce an elongate collar of bone (2nd stage). Externally, through activity of the osteoblasts in the periosteum, the enveloping shell of periosteal bone lengthens and thickens (3rd stage). Internally, spicules of endochondral bone and associated marrow tissue replace the original cartilage. Thus the tibia increases in calibre. At this stage bone formation is augmented by an auxiliary histological mechanism for longitudinal growth, namely, the secondary ossification center (4th, 5th

stages). One center appears before birth (ninth month); the other in the second postnatal year. In both of them cartilage persists as a growing plate: distally until the individual is 17 years of age, proximally through the 19th to the 23rd year (last stage). When epiphyseal cartilage is replaced by bone, growth ceases. Cartilage remains only on the articular surface of each extremity.

Recalling the above accounts of development, the following points of difference will be recognized as important.

1. Unlike a typical long bone, the otic capsule arises from numerous (14) ossification centers. The first develops in the fourth month (120 mm.) Three centers are soon present (Fig. 9, lower line of stages). Others appear in rapid succession, enveloping the labyrinth and replacing cartilage (2nd stage). They have fused to form a complete box prior to the middle of intra-uterine life (3rd stage).

2. The capsule forms a box to house sensory organs, developing to cover and surround the system of labyrinthine tubes.

3. Differing in structure from a long bone, epiphyseal areas are wanting in the capsule; there are no secondary centers of ossification.

4. Capsular development is exceedingly rapid; in a short period of three weeks the osseous capsule has been formed. The labyrinthine spaces of the capsule have attained adult dimensions at the middle of intra-uterine life (last stage). On the contrary, a tibia does not reach full size until the individual is twenty or more years of age (upper line, last stage).

5. Although the otic capsule of the midterm fetus is as large as it will ever be, it is not histologically mature. In attaining maturity, the endochondral tissue, in the core of the capsule (between periosteal and endosteal layers) is not removed (as it would be in a typical long bone) to make way for marrow. It remains as a tissue of petrous nature; it is composed of cartilaginous spicules, ossified, upon which osteoblasts have deposited bone to the almost complete obliteration of marrow.

6. Concurrently the periosteal bone, added to the capsule in the latter half of fetal life, is removed to make way for the pneumatic spaces of the apical and related portions of the temporal bone.

A tibia, as we have seen, grows steadily until the individual has reached maturity (Fig. 10, upper set). In an adult person the tibia is 36 times as long as it was when it made its first appearance

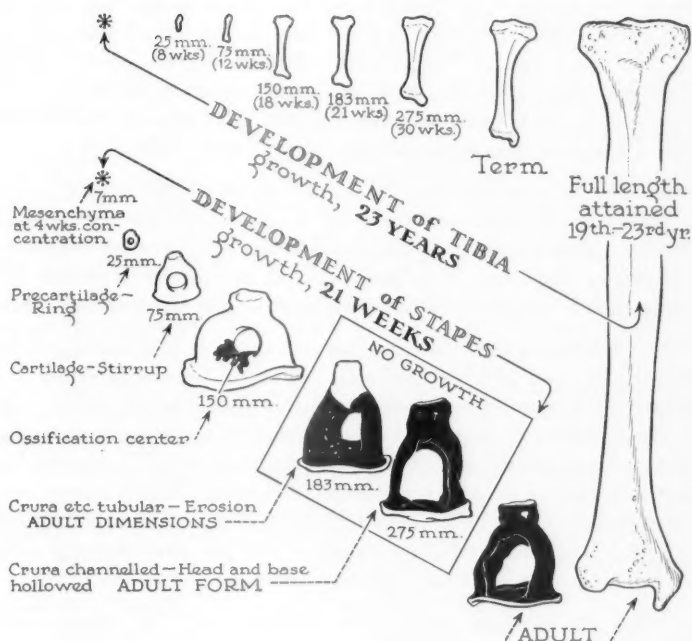


Fig. 10.—Comparative development of the stapes and the tibia. Diagrammatic.

in cartilage. At first, like a long bone, the stapes begins as cartilage, but is annular (Fig. 10, lower line, 2nd stage). Otherwise a stapes differs strikingly from a long bone, and specifically on the following counts:

- a. At first it is ring-shaped, then assumes the form of a stirrup.
- b. Ossification takes place from a single center (3rd stage). In this respect, too, the stapes differs from the capsule.
- c. Once formed in bone, the stapes does not become thicker, there being no external application of bone to the periosteal layer. And, in the stapes, production of endochondral bone is confined to the internal wall of the head and base of the ossicle.
- d. The stapes does not lengthen after periosteal bone has become continuous around the obturator foramen in the fifth month,



there being no epiphyseal, or secondary, centers for longitudinal growth (4th stage). In this regard, the ossicle is like the capsule. Thus, while a tibia continues to grow into the period of early adulthood, the stapes attains "adult" dimensions about the time a fetus has reached the half-way mark in its intra-uterine existence. By the same date the capsule becomes full-sized. Within a two-month period thereafter the stapes attains adult form (5th stage).

e. Unlike a typical long bone, one entire surface—that facing the obturator foramen—is removed continuously in the capital, crural and basal portions of the stapes. Marrow, in what would be the shaft, or diaphysis, of a long bone, is completely removed and is replaced by tympanic mucous membrane and submucosal tissue.

f. Whereas a tibia becomes heavier while it is maturing (progressively into the 20th or 23rd year), a stapes loses bulk while it is attaining maximum dimensions and adult form, in the fetus (4th and 5th stages). A stapes is far less robust as a mature ossicle than it was as fetal cartilage (compare 150-mm. fetus with adult). In losing substance, half of its periosteal shell is sacrificed; almost none of the endochondral bone is spared destruction. Concurrently, in the capsule the periosteal bone thickens and the endochondral bone increases to become a solid "petrous" core.

Thus it is that, while the capsule and the stapes both follow unusual developmental steps, each is peculiar in its own way. This, while lending additional attraction to otological studies, might puzzle the investigator who would interpret pathological changes only on a familiar osteogenetic basis.

#### SUMMARY

Based upon a study of approximately 300 series of sections, the authors have described the developmental history of the otic capsule, of the extracapsular layer of bone, and of the auditory ossicles.

Supporting the text descriptions, major stages have been illustrated by means of drawings of selected sections and of reconstructions. In addition, the histogenesis of the middle layer of capsular bone has been described and illustrated in particular detail.

Finally, the developmental steps have been compared with those more conventional stages in the formation of a typical long bone, the chief differences being illustrated in sets of diagrammatic figures.

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COMPLICATIONS FOLLOWING IRRADIATION OF THE  
THYROID GLAND

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X-ray irradiation of the larynx for carcinoma is justified in cases of inoperable cancer and as after-treatment in those cases in which there is a question of remaining concealed cancer cells.

However, when x-ray is resorted to in treatment of other conditions in close proximity to the larynx and trachea (notably lesions of the thyroid gland), much consideration must be given to the possibilities of damage to the underlying larynx and trachea.

"Among roentgenologists, irradiation of the thyroid gland for exophthalmic goiter, hyperthyroidism, etc., is considered definitely indicated; however, the dosage must be controlled and filtration properly applied. Over-dosage must be strictly guarded against. The object of the treatment is for physiologic effect only and any dosage or length of irradiation which will produce organic change must be guarded against. Prolonged or intensive irradiation of the thyroid gland for goiter is unjustified. For surgical diseases of the thyroid, such as benign tumors and cysts, x-ray treatment is not indicated."<sup>1</sup>

When indiscriminate use of irradiation is made in trying to cure the diseased thyroid gland, damage can be done to the underlying larynx and trachea. The damage done to these organs is permanent and will require a lifetime of treatment. In addition, the patient is constantly in danger of death due to asphyxia. In the cases herein reported, obstruction to the airway was due, not only to pathologic narrowing of the larynx and trachea, but also was due to altered secretion accumulating at the point of stenosis.

Indeed, one patient lost her life because crusts became wedged in the narrowed airway during the night and help could not be obtained quickly enough to save her life.

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From the Bronchoscopic Clinic of the Jefferson Hospital.

Cartilages of the larynx and trachea are susceptible to intensive irradiation. Jackson<sup>2</sup> has said in reference to irradiation for the cure of laryngeal papilloma that "in using radium and the roentgen ray, the slightest overdosage will end in disastrous perichondritis, necrosis, stenosis, or sloughing."

Clerf<sup>3</sup> has shown that extensive irradiation of the thyroid gland for exophthalmic goiter produces telangiectasis of the skin over the front of the neck with subcutaneous changes in which the blood vessels are degenerated, rendering the subcutaneous tissues avascular and destroying the muscles in the region of the trachea. An immediate emergency tracheotomy resulted in sloughing of the tracheotomy wound due to necrosis and gangrene of the devitalized tissues.

In 1927, Clerf<sup>3</sup> reported in addition to four cases of papilloma of the larynx treated by irradiation, two cases of exophthalmic goiter treated by irradiation. Both of the patients with goiters required emergency tracheotomies on admission. The tracheotomy wounds sloughed because of the devitalized pretracheal tissues. In the one case, death ensued and in the other case, healing finally was slowly accomplished after a stormy convalescence in which infection and necrosis had to be combatted.

Changes taking place in the neck and the trachea are not at once apparent. X-ray films usually are of little or no help, as they generally are negative. Change may start as a tracheobronchitis which does not clear up but progresses to definite localized lesions. The degenerative process is slow and may not give alarming symptoms until several years later and the damage is permanent and progressive.

Epithelium desquamates and gland functions are either changed or destroyed, resulting in altered tracheal secretion which is not moved readily by ciliary action and adheres to eroded and granulomatous surfaces. Crusts constantly form and are attached to the damaged areas. Proliferation of granulation tissue and in some cases definite hemangiomatic lesions produce stenosis. The dyspnea due to the stenosis is markedly increased by the thick secretions and crusts collecting about the stenosed area.

#### REPORT OF CASES

CASE 1.—E. G., white female, aged 48, received very intensive x-ray treatment for nearly one year for exophthalmic goiter eight years before admission to the hospital. Following this treatment, her breathing gradually became difficult and the dyspnea steadily

increased until at the present time she is unable to lie down at night. Three years ago, a bronchoscopy was performed at another hospital which revealed stenosis of the upper trachea. The patient refused tracheotomy, which was advised at that time. Since then, she has developed a cough with expectoration of blood and pus, which varied in quantity, some days there being as much as a quarter of a cup. At times, the blood is bright red; at other times, it is dark and clotted.

She was admitted to the Bronchoscopic Clinic of the Jefferson Hospital seven years after the irradiation of the trachea.

Examination showed very marked inspiratory dyspnea with an inspiratory stridor. The nose, mouth, and throat were negative. On mirror laryngoscopy, the larynx was negative except that there appeared to be a narrowing of the trachea about the second ring. The neck showed marked telangiectasis, particularly on the right side. X-ray studies showed no distinct evidence of any mass compressing the trachea. Wassermann and Kahn tests were negative.

A diagnostic bronchoscopy was performed. At about the level of the second or third tracheal ring, there was found a marked narrowing of the tracheal airway, the result of a large granulomatous mass, which was attached to the anterior wall of the trachea. An inspissated mass of secretion was found adherent to this. Following removal of the mass of secretion, the lumen could be visualized. This appeared crescentic. No attempt was made to investigate the trachea beyond the point of stenosis. It is not certain whether the stenosis was the result of inflammatory tissue or whether there were extensive cicatricial changes. It was thought inadvisable to pass the bronchoscope through the stenosed lumen because of the development of postendoscopic swelling of the mucosa which would have necessitated a tracheotomy.

The following day, a tracheotomy was performed for relief of the dyspnea.

Two days later a second bronchoscopy was done, at which time it was seen that the lumen of the trachea was not larger than 8 mm. at the point of stenosis. The granulation tissue causing the obstruction was removed with great improvement in breathing. The laboratory report on the granulation tissue was: fibro-angioma of the trachea.

The stenotic area was dilated with round tracheal dilators after the granulations stopped forming, and the patient was discharged, definitely improved, to the care of her family physician.

Eight months later, the mucosa of the trachea showed a granular and inflamed area which had appeared just below the previously healed portion of the trachea after her discharge from the hospital. In the meantime, the patient had been expectorating blood-tinged sputum at irregular intervals. These granulations were removed by bronchoscopy.

One and a half years later, she was readmitted, complaining of loss of seven or eight pounds in weight, and aching pains in both ears and across the chest. During the past three months, she had had choking attacks followed by hemoptysis. She stated that on one occasion she brought up a pint of blood.

Bronchoscopy revealed a narrowed, oval-shaped lumen immediately beyond the larynx with granulations on the anterior and right lateral walls at the narrowest portion. The stenosis reduced the lumen of the trachea to about one-third its normal width. Auscultation of the chest elicited whistling sounds transmitted along the bronchi and into both upper lobes.

Four years later, a small granuloma was removed from below the point of stenosis. The laboratory reported this to be inflammatory tissue. A tracheotomy was necessary. There was relatively little bleeding during the tracheotomy.

Two and one-half years later, a letter was received from her family physician stating that the patient was suffering from pain in the larynx and tracheal region, and hemoptysis followed by severe pain. The patient needed repeated doses of Pantopon for relief. There is a question of a malignant growth developing in the stenotic area.

CASE 2.—I. B., female, aged 31, received deep roentgen therapy to the thyroid gland six years before admission to the Jefferson Hospital in 1937. Three years later, she had an attack of aphonia following what she thought was an acute upper respiratory infection. Shortly after this, she developed inspiratory dyspnea, which has persisted and become more marked so that the patient has become unable to do hard work or exert herself. She developed cough and wheezing with expectoration of fetid, mucopurulent material with occasional greenish lumps. She has been under the care of many physicians who have made various diagnoses. She had two bronchoscopies at another hospital in 1936 at which time an autogenous vaccine was made and given without improvement. A diagnosis of tracheobronchitis was made. A roentgenogram of the



chest in July 1937 was said to be negative. The Wassermann test was negative.

The patient was admitted to Jefferson Hospital on December 3, 1937, with distressing inspiratory dyspnea and an irritative cough. The mucosa of the larynx was moderately congested and large dark crusts were observed by mirror laryngoscopy in the trachea, probably 3 cm. below the level of the cord. There was moderate telangiectasis with some scarring on the front of the neck, apparently the result of irradiation.

The day after admission, a tracheoscopy was performed revealing a marked narrowing of the trachea, the lumen of which was not greater than 1 cm. in its transverse diameter. The narrowing began at the third tracheal ring and extended downward for about 1 cm. There was a granular ulceration of the mucosa with slight bleeding on the posterior wall. Marked crusting was present.

The patient was treated by intralaryngeal instillations of medicated oil with considerable improvement.

Several readmissions to the hospital were necessary over a period of ten years to remove the crusts from the trachea. She had repeated attacks of marked dyspnea due to crusting and it was necessary to instill salt solution to remove the crusts. Bronchoscopy was necessary on several occasions to remove the crusts from the narrowed trachea.

A bronchoscopy was performed one year ago to remove crusts, and it revealed a proliferating mass on the left wall of the trachea, which appeared to be either malignant or granulation tissue. Laboratory examination showed it to be hyperplastic epithelium.

Oil instillations were discontinued and physiologic sodium chloride solution was substituted to avoid lipoid pneumonia.

In January 1948, the patient awakened at 1:00 p.m. and was aphonic. She awakened her sister-in-law and pointed to her throat. She died before a conveyance could be obtained to take her to a hospital.

This case exhibits atrophic changes in the mucosa due to irradiation. Ciliary action of the epithelium evidently was destroyed and destruction of the epithelium, resulting in ulceration and excessive granulation formation, produced stenosis. Secretions became excessive and stagnant, resulting in crusting. The big problem was controlling the formation of crusts. Instillations of saline solution

helped, but bronchoscopic removal was necessary at irregular intervals. In the meantime, the patient was in constant danger of asphyxia and finally died from it.

CASE 3.—G. M., white female, aged 40, was admitted to the hospital in 1939 complaining of burns to her neck following extensive x-ray therapy in 1931. She had a sense of something in the throat when swallowing and on speaking for a time. In 1931 a diagnosis of goiter had been made, for which extensive x-ray therapy had been given by a nose and throat specialist. Treatments were given once a month for a year. Recently the scars on the front of the neck, which resulted from the treatment, have been troubling her and she is becoming throat conscious ("senses something in the throat"). There was no weight loss and no pain; her voice was not affected.

Physical examination showed the patient to be well developed and nourished. There was no hoarseness and no wheezing. The larynx was negative. There was a rectangular area of telangiectasis 3 x 4 in. in size on the front of the neck. It extended slightly more to the right and exhibited more thickening and induration on the right side. There were present a number of firm areas which suggested keratosis. It was difficult to palpate structures beneath the skin in this location. There were excrescences on the affected area.

Seven years after the irradiation, bronchoscopy showed a narrowing of the trachea due to an extratracheal lesion on the anterior and right tracheal walls, which was encroaching on the tracheal lumen. There was a narrowing at a point about 3 or 4 cm. below the level of the larynx, a crowding inward of the anterior and right lateral wall, though this was not sufficient to interfere with an adequate tracheal lumen. The mucosa of the entire trachea was found moderately congested, no ulceration was observed and the remainder of the air passage appeared normal.

Esophagoscopy showed nothing abnormal. The patient was discharged from the hospital in November 1939.

The patient was seen in September 1947 at her doctor's office. At that time she was having slight increase of dyspnea and apparently also some difficulty with crusts accumulating in the trachea. There was some breaking down of the superficial epithelial layers of the front of the neck. Her general condition was satisfactory.

CASE 4.—I. C., white female, aged 43, complained of hoarseness for the past two years with occasional shortness of breath. She had a toxic thyroid removed 12 years before admission. Following

this, a long course of irradiation therapy was received. Report of the biopsy of the gland, left side, was: question of malignancy.

Two years after receiving irradiation therapy for a year, the patient became hoarse and dyspneic. This persisted and seven years later she had two growths removed, one from each vocal cord. Following this, her voice was clear for two years. However, hoarseness gradually returned.

Physical examination showed the voice moderately hoarse. There was no dyspnea. The motility of the larynx was good. The vocal cords were thickened, granular and red, suggesting telangiectasis in their anterior halves. There were no ulcerations present. There was marked telangiectasis of the skin of the neck, with considerable thickening over the trachea.

She was discharged definitely improved.

One month later, there was a large quantity of very thick tenacious secretion adhering to the posterior commissure which was dislodged by instillation of physiologic sodium chloride solution. The right vocal cord showed hemorrhage throughout its entire extent; the left vocal cord was quite red and exhibited crusting. Instillations of saline solution were required to remove crusting and secretions.

The patient was readmitted in December 1946. She was aphonic and moderately dyspneic. These symptoms developed following a recent respiratory infection. There was marked crusting on both vocal cords. Following removal of crusting by saline solution, a small elevation was observed on each vocal cord at the anterior third, the nodule on the right cord being more anterior than the one on the left cord. In December 1946 these elevations were removed by direct laryngoscopy. The laboratory report on the biopsy was hyperplastic epithelium.

For the past year, intralaryngeal instillations of physiologic sodium chloride solution have been required to rid the trachea of thick stagnant secretions which hamper respiration.

At the present time, there is still some hoarseness. Examination of the larynx reveals inflammatory thickening of the right vocal cord but no evidence of nodulation. There is no impairment of motility and the airway is adequate. The neck exhibits telangiectasis with subcutaneous fibrosis, so that the entire front of the neck is firm and it is impossible to determine the exact site of the trachea.

This is another incident of extensive irradiation therapy.

CASE 5.—R. P., white female, aged 31, was in good health until five years before admission to Jefferson Hospital in September 1944, when she began to have a palpitation of the heart and nervousness. A diagnosis of hyperthyroidism was made. One year later, her thyroid gland was treated by irradiation. This was followed by telangiectasis on the anterior aspect of the neck, shortness of breath, swelling of the ankles, and it became necessary for her to sleep with her head elevated. Two years before admission to Jefferson, she became hoarse. The condition became worse with a feeling of tightness in the throat and dysphagia. She had frequent sore throats. In the past few weeks, hoarseness and dysphagia increased with a loss of weight of seven pounds. The patient had been taking iodine, but had taken none during the past several months. Symptoms of hyperthyroidism had persisted.

Mirror laryngoscopy showed stenosis of the larynx due to a proliferating subglottic lesion, with complete obliteration of the anterior third of the glottis. There was also some change in the posterior commissure. As a result, the airway was oval in shape and occupied about 25 per cent of the normal glottis. Motility of two sides of the larynx was quite satisfactory. There was marked telangiectasis of the front of the neck. The x-ray film showed no evidence of retrosternal thyroid. Wassermann and Kahn tests were negative.

Shortness of breath gradually became more marked, and the patient did not respond to medical treatment at home. Chest expansion was equal; there was impairment of the percussion note in both lower lobes anteriorly and posteriorly, and wheezing breath sounds throughout.

A tracheotomy was performed and the tissues were found to be more or less avascular. As soon as the trachea was opened, the patient coughed up a large clump of thick secretion. X-ray examination was negative and did not show anything to suggest stenosis, but after instillation of iodized oil, a short, narrow constriction of the tracheal air column immediately below the thyroid cartilage could be made out.

Under direct laryngoscopy an incision was made with the laryngeal knife along the left margin of the web practically to the anterior commissure. Laryngoscopic dilatation was done, four days later, with No. 20 triangular bougies through the narrowed laryngeal lumen, and the airway became definitely larger than formerly.

In December 1944 the patient was discharged to return to her physician. When she was seen one and a half months later, her voice was good and the laryngeal airway seemed ample. The left vocal cord had remained intensely red, and the right cord was almost normal. Part of the web anteriorly had reformed, particularly subglottically.

A second incision by direct laryngoscopy was carried along the left vocal cord extending to practically the anterior commissure, and a complete cork was used in the tracheal cannula.

Two months later, the cannula was removed because of satisfactory breathing through the larynx.

Seven months after decannulation, the patient again began to have difficulty with breathing and particularly with phonating. She had to clear her throat a good deal and had difficulty in getting rid of thick sticky secretion. Her general condition was satisfactory.

Mirror laryngoscopy showed a marked redness of the mucosa and thick secretion adhering to the vocal cords, ventricular bands, and epiglottis. Instillations of salt solution were necessary to remove the thick and adherent secretions. The front of the neck now exhibits slightly more induration of the telangiectatic areas, and treatment consists of intratracheal instillations of salt solution and 5 cc. of ephedrine sulfate instilled into the larynx daily.

Symptoms exhibited in the five cases recorded here are: hoarseness, sensation of lump in the throat, inspiratory dyspnea, wheezing, dysphagia, cough, expectoration, loss of weight, pain in chest.

The physical findings are: congestion of the laryngeal mucosa, telangiectasis and scarring of the neck, stenosis of the larynx, inflammation of the laryngeal mucosa, telangiectasis of the vocal cords, stenosis of the trachea, granulomatous lesion in the tracheal walls, crowding inward of the tracheal wall, viscid adherent tracheal secretions, crusting. Cicatrices are not common; only a suggestion of cicatricial tissue was present in one case.

Tracheotomy was required in three cases.

The time between termination of the irradiation and appearance of the first symptoms of tracheal disease was from one year (2 cases), to three years (2 cases), to seven years (1 case).

The patients have been under continuous treatment for relief of symptoms for one year (1 case), three years (1 case), nine years (1 case), ten years (1 case), and eleven years (1 case).

While the irradiation is not aimed at the larynx or the trachea, these organs will suffer from excessive or extensive irradiation of the thyroid gland. Not only may the tissues of the larynx and trachea be altered by the rays, but the overlying tissues will be damaged by changes in the blood vessels and lowered resistance to infection so that operative procedures (tracheotomy) become hazardous. Not only is healing of the operative field retarded or prevented by the devitalized tissues, but resistance to infection is lowered, resulting in some cases in necrosis and gangrene of the operative field.

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LVI

HAND-SCHÜLLER-CHRISTIAN DISEASE AND  
EOSINOPHILIC GRANULOMA OF  
THE SKULL

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Destructive lesions of the skull occurring as a primary feature in a disease may present a diagnostic problem. The xanthomatous diseases must be considered. These are Hand-Schüller-Christian<sup>1, 2, 3</sup> disease and its related conditions. Our experience deals with seven cases in this group. Three of these patients had initial destructive lesions of the temporal bone and their conditions are classified as Hand-Schüller-Christian disease. The remaining four patients had solitary granulomas elsewhere in the skull.

It is now evident that there are two conditions which are intimately related to Hand-Schüller-Christian disease. They are Letterer-Siwe disease<sup>4, 5</sup> and eosinophilic granuloma. They are now considered to be clinical gradations of expression of the same basic disorder underlying Hand-Schüller-Christian disease. Letterer-Siwe disease is a more severe type and eosinophilic granuloma is a milder form.

The etiology of Hand-Schüller-Christian disease is not known. It has been generally considered to be a lipid storage disease. To support this view is the common finding of large amounts of cholesterol in the lesions. Several factors, however, tend to refute the idea of this being a lipid storage disease. If this were a lipid storage disease, one would expect the concentration of blood lipoids to be elevated; however, significant elevations are exceptional. Storage of cholesterol in the tissues, induced by feeding it in large

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amounts to rabbits, does not produce a lipogranulomatous lesion as seen in Hand-Schüller-Christian disease. Also, there is no racial or familial tendency as in the other lipid storage diseases (Gaucher's disease and Niemann-Pick disease). Since Hand-Schüller-Christian disease has been linked with Letterer-Siwe disease and eosinophilic granuloma, the theory has been advanced that these diseases are all due to some infectious agent. In this regard, the inflammatory character of the lesions is thought to be significant. It can, of course, be argued that a chemical irritant such as lipid can also produce an inflammatory lesion. Extensive bacteriological, virus, and fungus studies have failed to reveal any constant etiological agent. That the lesions respond dramatically to irradiation seems significant. This phenomenon can be held to favor the theory that the etiology is a disturbance in cell metabolism resulting in lipid storage.

The clinical and pathological features of these disease can be described as follows:

*Letterer-Siwe Disease* (non-lipoid histiocytosis, reticulo-endotheliosis, reticulosis). That Letterer-Siwe disease and Hand-Schüller-Christian disease are variant expressions of the same basic disorder and closely related anatomically has been advanced by Wallgren<sup>6</sup> and others.<sup>7,8</sup> Letterer-Siwe disease is a rapidly fatal condition usually occurring before the age of two. The principal clinical findings are enlargement of the liver, spleen, and lymph nodes, secondary anemia, purpuric cutaneous eruption, destructive skeletal lesions, especially in the skull, and a rapidly downhill, acute, febrile course.

The histopathology consists of nodular and diffuse collections of histiocytes throughout the lymphatic system, many viscera, and bone marrow. The early skeletal lesion may closely resemble those in eosinophilic granuloma, being characterized by sheets of histiocytes and interspersed groups and scattered eosinophiles. Also, the older lesions, when seen in children who live beyond the age of four, may contain lipid-filled histiocytes and closely resemble the histopathological picture of the lesions seen in Hand-Schüller-Christian disease.

*Hand-Schüller-Christian Disease* (lipoid granulomatosis). Originally the term Hand-Schüller-Christian disease was applied to those cases in which the triad of diabetes insipidus, exophthalmos and calvarial defects were present. We now know that the symptoms of diabetes insipidus and exophthalmos are only dependent on involvement of the sphenoid bone and the bones limiting the orbit.

The term Hand-Schüller-Christian disease is commonly used whether the triad is present or not. We will use it here although fully realizing certain objections to its use. The early skull lesions may involve the temporal bone and result in disturbances in and around the ear before other symptoms occur. When part or all of the triad of diabetes insipidus, exophthalmos, and calvarial defects are present, the diagnosis is not difficult. The true nature of the process is not so obvious, however, when there is only an aural discharge and roentgen findings of a destructive lesion of the temporal bone. Mastoidectomy is frequently performed in these cases before the correct diagnosis is suspected. This happened in two of our cases. When one realizes that x-ray therapy is the treatment of choice and that surgery should be used only in the event of a complicating infection or possibly for biopsy, the importance of making an early correct diagnosis becomes obvious. In 1923 Grosh and Stifel,<sup>9</sup> in reporting the seventh case of Hand-Schüller-Christian disease to appear in the literature, describe in a 6-year-old child onset of discharge from the ear without pain for which a mastoidectomy was done. The patient later developed the complete triad of diabetes insipidus, exophthalmos, and calvarial defects as previously described by Schüller. Greifenstein<sup>10</sup> reviewed 26 cases of Hand-Schüller-Christian disease appearing in the literature up to 1932 and noted that the ear was involved 12 times, the maxilla 13 times, and the paranasal sinuses 5 times.

The disease usually appears in childhood; however, it may occur in the second or third decade of life and even later. Initial symptoms may consist of the appearance of exophthalmos, diabetes insipidus, or tender areas over the skull. However, other symptoms such as stunting of growth, discharge from the ear due to mastoid involvement, anemia and loss of energy, pathological fractures, adiposity, or hypogenitalism may be the first to appear. In addition to the skull lesions there may be osteolytic lesions in the long bones, scapula, and ribs which are often accompanied by aching pains. Diffuse infiltrative lesions of the liver and spleen may result in mild enlargement of these organs. The lungs and heart may also be involved. The characteristic pulmonary lesions are demonstrated radiographically by soft shadows extending out from the hila. The meninges, brain, and spinal cord may also be the site of such infiltrations. A cutaneous eruption is not uncommon and biopsy of the skin demonstrates the characteristic lipophages. In some instances the peripheral blood may show a mild eosinophilia. In a small percentage of the cases cholesterol and cholesterol esters are slightly elevated in the blood.

The mortality rate in Hand-Schüller-Christian disease is about 30 per cent. The prognosis is poor in those cases occurring early in life and those having involvement of the visceral, neural, or endocrine organs. Right heart failure secondary to extensive pulmonary fibrosis has been reported to be a cause of death.<sup>11</sup> The principal feature of the lesions is the presence in them of sheets and strands of lipoid-filled histiocytes (foam cells). The lipoid is cholesterol and cholesterol ester. Grossly this tissue appears as a yellowish-grey granulation tissue. In some instances, however, the microscopic picture is that of a granulomatous tissue. The predominant cells are the histiocytes, a few of which may have united to form multinucleated giant cells. Many of the histiocytes may not contain lipoid; however, one usually can find areas containing the characteristic foam cells. There are areas having numerous polymorphonuclear leukocytes which may be predominantly eosinophiles. Areas of necrosis and hemorrhage are common.

*Eosinophilic Granuloma (solitary granuloma of bone).* Eosinophilic granuloma which is the mildest form of the disorder manifests itself as one or more benign lesions of the skeleton. Thannhauser,<sup>12</sup> Chester,<sup>11</sup> Frazer<sup>13</sup> and Rowland<sup>14</sup> were apparently aware of the occurrence of a monosymptomatic early stage of Hand-Schüller-Christian disease a decade or more ago. For some years a peculiar form of eosinophilic osteomyelitis was known to exist when in 1940 Otani and Ehrlich<sup>15</sup> described the condition under the name of "solitary granuloma of bone." Simultaneously Lichtenstein and Jaffe<sup>16</sup> reported similar cases under the title "eosinophilic granuloma of bone." Hatcher<sup>17</sup> and Mallory<sup>18</sup> reported more cases using the term "eosinophilic granuloma of bone." The latter term is now used popularly with few exceptions.<sup>19</sup>

Green and Farber<sup>20</sup> reported on ten cases in 1942; four of these patients had single lesions and six had multiple lesions. They pointed out the close relationship of this destructive granuloma to Letterer-Siwe disease and Hand-Schüller-Christian disease and emphasized that the prognosis in the individual case must be guarded for this reason.

The name eosinophilic granuloma probably should apply only to mild cases of the disorder which manifest themselves in the form of one or a few skeletal lesions without accompanying visceral, neural, or cutaneous involvement. That many cases will fall in a category midway between this benign form and the more serious Hand-Schüller-Christian disease is apparent from reports appearing in the literature<sup>21, 22</sup> and our Case 3.

Eosinophilic granuloma is usually seen in children or young adults. Silliphant and Hull<sup>23</sup> recently stated that 80 per cent of the cases now appearing in the literature occurred in patients under 30 years of age. Most commonly affected are the long bones, skull, ribs and vertebrae. Local pain and tenderness are the usual presenting symptoms. There may be impaired function if the lesion occurs near a joint. Systemic symptoms do not occur. Roentgenographically the lesion appears as a sharply delineated radiolucent zone in the bone. As the lesion grows, the cortex may be expanded. Erosion through the cortex, as the outer table of the skull, will be accompanied by swelling and tenderness of the overlying soft tissue. There is nothing about the roentgenographic appearance of the individual bone lesions in eosinophilic granuloma and Hand-Schüller-Christian disease which will differentiate them from each other.

The microscopic picture is that of sheets and strands of histiocytes, scattered throughout which are the striking collections of eosinophiles. The histiocytes usually have a single nucleus, but may have two or more. The eosinophiles are small and may have lobulated, indented, or round nuclei. Areas of necrosis and hemorrhage are often found. Giant cells may be present in such areas.

Grossly the granulation tissue is yellowish-grey or brown, depending on the degree of necrosis and hemorrhage present.

*Pathological Similarity of These Diseases.* — Hand-Christian-Schüller syndrome may appear in certain more chronic cases of Letterer-Siwe disease. In such cases the cell structure of the lesions passes from a proliferative into a characteristically lipoid or xanthomatous phase. Further, although the structure of the various lesions in an individual case of Hand-Schüller-Christian disease is fairly uniform, it may vary between different cases. In particular are those mild cases which have multiple lesions but minimal visceral involvement and which have a granulomatous rather than the usual xanthomatous lesions. Such cases appear to fall midway between Hand-Schüller-Christian disease and eosinophilic granuloma.

The degree of chronicity and severity of the basic disorder is roughly reflected in the histo-anatomical structure of the lesions. The phases in which the lesions may manifest themselves are listed below after the concepts of Green and Farber<sup>20</sup> and later Holm, Teilem and Christensen.<sup>24</sup> It is not implied that the lesions develop or heal by passing step by step through these various phases. Jaffe and Lichtenstein<sup>25, 26</sup> and Hatcher<sup>27</sup> have pointed out, in fact, that there is yet no evidence to show that the healing eosinophilic granuloma passes through a xanthomatous phase.

1. Proliferative Phase: The basic histological component of this phase is the histiocyte which appears in strands and sheet-like collections. Some of these histiocytes are actively phagocytic and some are multinucleated. There may also be groups and scattered eosinophiles and occasional lymphocytes and plasma cells.

2. Granulomatous Phase: There is an increase in blood vessels and stroma. The histiocytes continue to proliferate and there are conspicuous collections of eosinophiles. Giant cells are more frequently seen. Areas of hemorrhage and necrosis may be present. A few scattered lipophages may be found.

3. Xanthomatous Phase: The presence of lipophages (foam cells) earmarks this stage. These lipoid-filled histiocytes usually appear as round cells with small oval or round nuclei and have a surrounding finely vacuolated or foamy cytoplasm.

4. Fibrous Phase. This is the final healing stage. The more cellular elements are replaced by fibrous connective tissue which in the case of skeletal lesions may be transformed into bone.

In Letterer-Siwe disease the histopathological picture of the bone lesions is that of the proliferative or granulomatous stages. If the patient survives long enough, the lesions may become xanthomatous.

Hand-Schüller-Christian disease is characterized by the presence in the lesion of large numbers of lipophages, representing the xanthomatous phase. In eosinophilic granuloma the lesions are characteristically granulomatous. The finding of an occasional lipophage in an eosinophilic granuloma does not necessarily represent a xanthomatous change in the lesion, as lipophages are commonly found in chronic granulation tissue.

#### REPORT OF CASES

The following cases demonstrate the varied symptomatology and course of the diseases and the problems involved in diagnosis and treatment.

CASE 1.—B. H., age 30.

*History:* This 30-year-old male was first seen on April 6, 1938, at which time he complained of having had: mild, right ear-ache three months previously with slight discharge lasting one week; dizzy spells for the previous three months, coming on when he sneezed, blew his nose, or made sudden postural changes; hissing

noise in the right ear for the previous six weeks; poor hearing in the right ear for three months. There was no pain in or around the ear and at no time in the past winter had he had an upper respiratory infection or felt ill. He had occasional pains in the right shoulder and over the left anterior superior iliac spine for three months.

*Examination:* The right tympanic membrane was intact and of normal contour; however there was slight injection along the handle of the malleus. Two small soft polypoid masses were seen projecting into the right external auditory meatus from the superior wall near the annulus and hiding Shrapnell's area and the short process. There was a yellowish exudate in the canal. There was no spontaneous nystagmus with the eyes in the mid-position. The fistula test was positive: positive pressure gave a nystagmus to the right and negative pressure a nystagmus to the left. Air conduction audiometry revealed a 50 to 70 db. loss for all tones in the right ear.

X-ray films revealed mottling, obliteration, and cyst-like areas in the right mastoid bone (Fig. 1a).

Direct smear from the right ear showed diphtheroids and many gram-positive cocci in groups. Peripheral blood counts were normal.

*Operation:* On April 13, 1938, a right radical mastoidectomy was performed. The mastoid cortex was found to be intact on the outer surface; however, the entire mastoid cavity was filled with a soft, grey granulation tissue-like material. The bony walls surrounding this mass were unusually soft. Most of the posterior canal wall, the bridge and roof of the canal wall, were entirely eroded away. A large amount of this granulation tissue was scooped out of the mastoid cavity and the mastoid tip was completely cleaned. Further removal of this tissue near the horizontal semicircular canal and facial canal was not attempted because pressure in that area caused right facial twitching and conjugate deviation of the eyes to the left. A Koerner flap was cut leaving a large opening from the external canal into the mastoid.

*Histopathology:* Because the diagnostic significance of the histopathological picture of this tissue was not realized originally, it was reported as being nonspecific granulation tissue. Its true nature was revealed to us, however, when re-examined later in the course of the disease after the diagnosis became obvious.

Throughout were sheets and strands of mononuclear histiocytes separated by areas of hemorrhage and necrosis. Eosinophiles were



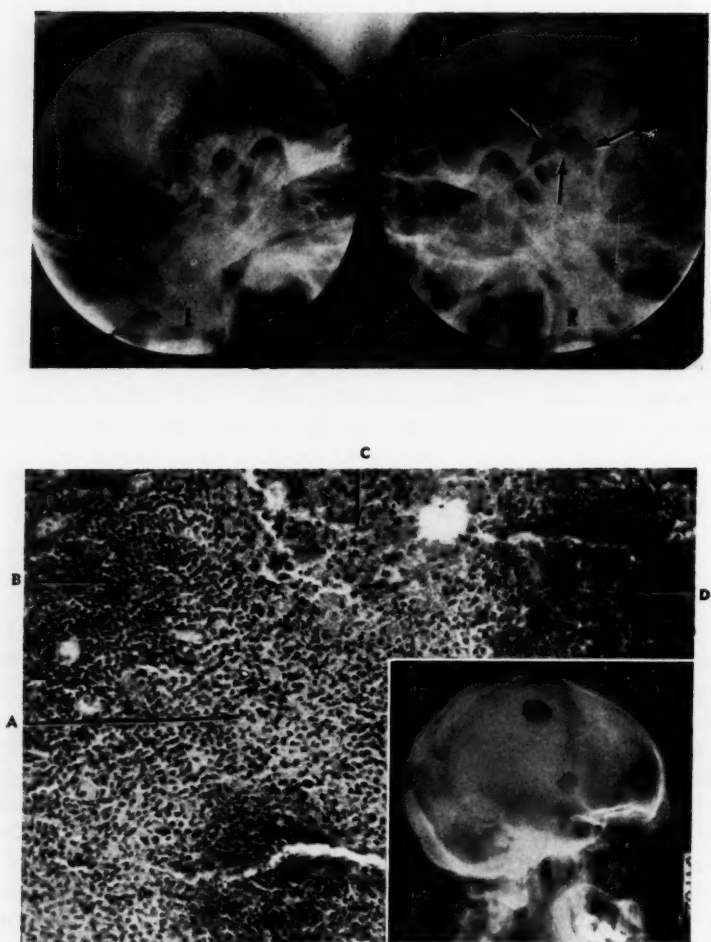


Fig. 1, Case 1.—*a*, Bullitt views demonstrating lesion of Hand-Schüller-Christian disease in the right mastoid (April 6, 1938). *b*, Tissue removed from mastoid lesion (April 13, 1938) A, Sheet of histiocytes; B, group of mononuclear and polymorphonuclear eosinophiles; C, area of hemorrhage; D, area of necrosis. *c*, Roentgenogram showing new lesions which appeared in the skull during the year subsequent to mastoidectomy (February 19, 1939).



scattered throughout among the histiocytes. In some areas they appeared in groups. The scattered eosinophiles had predominantly lobulated nuclei, whereas those appearing in groups had mainly round nuclei. Only in one area were a few scattered lipophages (foam cells) seen. Many small blood vessels were present (Fig. 1b).

*Clinical Course:* Postoperatively there was considerable exuberant granulation tissue in the mastoid cavity. The pains in the right shoulder and over the left anterior superior iliac spine of which the patient complained originally became more severe, and on May 12, 1938, x-ray films of the right scapula and pelvis were made. A small area of decreased density with mildly sclerotic borders was seen in the right scapula and three similar lesions in the pelvis.

Biopsy of the right scapula on May 20, 1938, and of a skull lesion on February 18, 1939, revealed the histological picture of this tissue to be identical with that in the mastoid.

The chest films taken during this period showed soft infiltrative lesions extending out from both hila. Deep x-ray therapy was given all lesions.

On December 9, 1938, the right mastoid cavity appeared improved and partial epithelization had taken place. However, there was now tenderness and swelling over the region of the zygomatic root and extending back as far as the occiput. There was drooping of the anterior superior canal wall. X-ray films of the right mastoid at this time revealed a multilocular lesion lying behind and above the operative site. On December 13, 1938, the mastoid was re-opened through a postauricular incision. A walled off pocket in the sinodural angle, having irregular granular margins and containing pus, was evacuated.

During the following four months the right ear became dry and completely epithelialized. During the following year, however, numerous new lesions appeared in the skull, pelvis, and ribs (Fig. 1c).

Deep x-ray therapy was given to all lesions as they appeared. The right temporal and parietal regions received 225 r and the left parietal region 670 r. The right lumbar regions received 1200 r in depth on two occasions 14 months apart. Other lesions received single short courses of between 1200 r and 1400 r at the lesion in each case. Technical factors for all treatments were: PKV 200; MA 20; Filter 1 mm. Cu., 1 mm. Al; HVL 1.5 mm. Cu; FSD 50 cm.; 37 r in air per minute.

*Diagnosis:* Hand-Schüller-Christian disease.

*Comment:* In this case the symptoms of a labyrinthine fistula prompted the patient to seek medical care. Perforation of the external auditory canal probably occurred three months prior to our first examination when he noted slight pain and discharge from the ear for one week. The presence of granulation tissue on the canal wall in the presence of an intact, fairly normal-appearing tympanic membrane, as occurred in this case and Case 3, is regarded as a highly significant diagnostic feature.

As has been pointed out by Shea,<sup>28</sup> healing of the mastoid cavity in such cases is very slow. In this case there was still profuse drainage from the ear six months after operation. It is unfortunate that the first operation was not avoided as it probably provided the route for infection which necessitated a second surgical procedure.

The occurrence of multiple skeletal lesions, the chronicity, and the pulmonary lesions indicate that this case should be classified as Hand-Schüller-Christian disease. Interesting is the fact that the tissue from three lesions, skull, mastoid and scapula, were in an active granulomatous phase, being identical with that seen in eosinophilic granuloma.

CASE 2.—J. B., age 22, male.

*History:* At the age of 12, and again at age of 17, this patient had left-sided earaches, and discharge lasting several days on each occasion and subsiding without sequelae. At the age of 22 on May 6, 1941, he developed a head cold and sore throat and three days later a left earache followed by drainage. Drainage from the ear continued. Four weeks after onset he noted sudden onset of dizziness which rapidly became very marked. He could not walk or stand and was nauseated and vomited occasionally. He remained in bed for two weeks during which time the vertigo gradually subsided. There continued to be a purulent discharge from the left ear during this entire period. On June 14 he developed a left facial weakness and entered a hospital. Three days after admission he began having more severe pain behind and in the ear and noted difficulty in swallowing for several days. The facial weakness subsided in three or four days. On the thirteenth day of hospitalization a left simple mastoidectomy was performed. During the following two weeks he had little pain, although the left ear as well as a postauricular fistula continued to drain. He then began having more severe pains in and around the left ear and in the frontal and occipital regions.

He was first seen at the University of Chicago Clinics on August 15, three months after onset of symptoms. At this time he had severe pains in the left side of the face, occiput, forehead, and left eye. There was no vertigo.

*Examination:* On examination there was found marked tenderness and slight swelling over the left zygoma and mastoid, and a postauricular fistula draining foul-smelling pus. The Weber test was referred to the right and the impression was that labyrinth function was gone. There was a small amount of pus in the left external auditory canal and a complete collapse of the posterior superior canal wall which obscured the tympanic membrane. The white blood count was 6,000; hemoglobin 12.0 gm. The nose, throat, chest, abdomen, and extremities were normal. No facial weakness was noted. He also had superficial tenderness and sharp pains in the area of distribution of the maxillary and mandibular divisions of the trigeminal nerve. Mastoid films taken on August 15, 1941, showed what appeared to be a non-pneumatized left petrous apex and marked bone destruction around the region of the internal acoustic meatus (Fig. 2 *a* and *b*). The operative defect of the mastoid bone was seen.

Visual fields revealed slight enlargement of the blind spot. There was a bilateral papilledema of 3 to 4 diopters in the left eye and 1½ diopters in the right.

Spinal tap on August 16 revealed a pressure of 170 mm. of water, 800 white blood cells (80% polymorphonuclears) and 70,000 red blood cells per cu. mm. (bloody tap?). Culture of spinal fluid grew staphylococcus albus.

Staphylococcus aureus grew from cultures of the ear.

*Operation:* On August 18, 1941, a left radical mastoidectomy was performed.

After the patient was anesthetized a spinal tap was done and clear fluid under 500 mm. of water pressure was encountered. Enough fluid was allowed to escape to reduce this pressure to normal.

The already draining postauricular incision was enlarged and the periosteum reflected over the edges of the mastoid cavity. A partially exenterated mastoid cavity was found. Further dissection of the mastoid was carried out. In the sinodural angle an abscess was encountered which extended into the posterior fossa between the dura and the occipital bone. The dura was covered with a thick reddish granulation tissue in this area. About one ounce of pus



Fig. 2, Case 2.—*a*, Hand-Schüller-Christian disease. Roentgenogram showing destructive lesion of the left petrous bone (August 15, 1941).  
*b*, Axial view of the same lesion in the left petrous bone (August 18, 1941).

was evacuated from this abscess. A sequestrum from the postero-medial aspect of the petrous pyramid was dissected from the dura and removed. The zygomatic root was taken down and the posterior canal wall and bridge were removed along with polypoid granulation tissue in the canal.

*Histopathology:* The specimen consisted of curettings of very vascular granulation tissue containing many histiocytes, arranged irregularly throughout a rather loose fibrous connective tissue stroma. Infiltrated throughout were also large numbers of polymorphonuclear leukocytes, about half of which were eosinophiles. Foam cells were present throughout, occurring singly or in small groups. Small areas of hemorrhage but no necrosis was seen (Fig. 3a).

*Clinical Course:* Postoperatively the pain in and around the ear was much less severe. The sharp pains over the areas of distribution of the mandibular and maxillary divisions of the fifth cranial nerve continued for two weeks and then subsided. The white blood count and spinal fluid pressure and cell count gradually returned to normal in two weeks. Three months postoperatively the mastoid cavity appeared healed. There was no cochlear or vestibular function in that ear.

Two months after the mastoidectomy he complained of pain in the right shoulder. An x-ray film of the right scapula on October 25, 1941, revealed a small osteolytic lesion (Fig. 3b). A block excision of the lesion was performed by Dr. Hatcher on December 3, 1941. Microscopic examination revealed a small bone lesion having a central cystic space surrounded by sheets and strands of round and polyhedral foam cells with small pyknotic nuclei (Fig. 3c).

Three months later a new lesion was noted in the frontal bone.

The patient was not cooperative and could not be followed or treated.

*Diagnosis:* Hand-Schüller-Christian disease.

*Comment:* This patient developed an acute otitis media in the left ear following an upper respiratory infection. After having aural drainage for two weeks, he developed an acute destructive labyrinthitis. Other structures involved as the process became more extensive were the facial nerve (transitory facial paralysis) the gas-serian ganglion (trigeminal neuralgia) and the tenth nerve (transitory dysphagia). A sequestrum involving a portion of the petrous pyramid was found at time of operation.

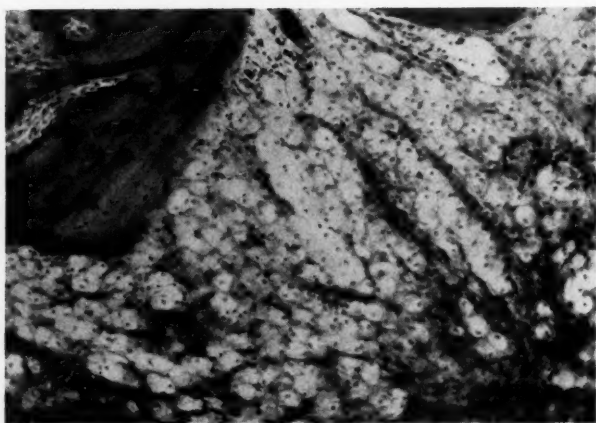
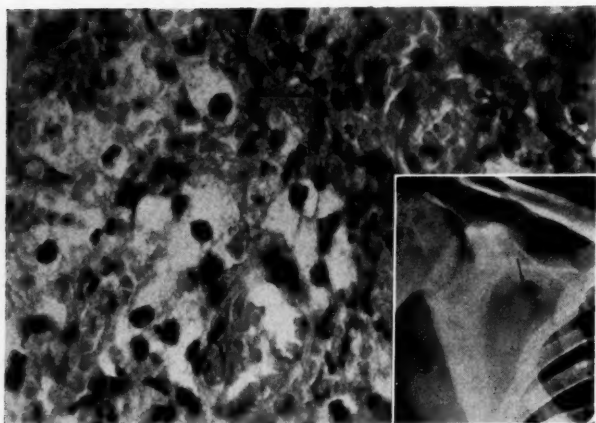


Fig. 3, Case 2.—*a*, Hand-Schüller-Christian disease (August 18, 1941). In a loose stroma are many small blood vessels, foam cells (arrow), eosinophiles, neutrophiles and lymphocytes. *b*, (inset) Subsequent to mastoidectomy a new lesion was found in the scapula (October 25, 1941). *c*, Tissue from scapular lesion showing the sheets and strands of foam cells.

Rosenwasser<sup>29</sup> reported a case in a 50-year-old woman who had a similar lesion of the temporal bone in which the initial symptoms were gradual onset of pain and deafness in the left ear of four years' duration. His patient also had transitory attacks of facial paralysis and complete loss of vestibular and cochlear function. In addition there was atrophy of the left half of the tongue and limitation of movement of the left vocal cord indicating that the tenth and twelfth cranial nerves had been involved.

McCaskey<sup>30</sup> had a case in which the facial nerve was involved. In his case there was still residual facial nerve weakness three years following mastoidectomy.

The cortex of the mastoid and the zygoma may be eroded away and result in swelling over these areas, either with or without infection. Lederer<sup>31</sup> and co-workers reported a case in which the first symptom of the disease in a two-year-old child was swelling over the zygoma. In Wood's<sup>32</sup> case there were bilateral postauricular swellings followed two months later by aural discharge. In that case mastoidectomies were performed which healed slowly. That sequestra may form in the petrous pyramid and mastoid is shown by our case, by the case reported by Glatt,<sup>33</sup> and the one by Cooper.<sup>34</sup> Cooper's case is interesting in that the initial symptoms of the disease in a three-year-old child were polyuria and polydipsia. Five weeks later postauricular swelling and aural discharge occurred with temperature and white blood count elevation. A simple mastoidectomy was performed. A roentgenogram revealed multiple skull lesions. X-ray therapy was given and the child was in good health two years later.

There appears to be a tendency for the lesions of Hand-Schüller-Christian disease of the temporal bone to become infected sooner or later. Because the primary lesion is often very extensive, the occurrence of a superimposed infection may be a serious complication. The route of infection in our case was probably by way of the eustachian tube from the infected respiratory passages. It seems probable that in some cases infection might occur via the external auditory canal after the canal wall is perforated by the lesion.

#### CASE 3.—E. P., age 2.

*History:* In March 1946 this two-year-old female had insidious onset of drainage of clear yellow fluid from the right ear. No fever and no pain was noted at any time. She entered another hospital in April and was given penicillin parenterally for two days (dosage not known). The drainage continued and on July 30, 1946, she





Fig. 4, Case 3.—*a*, Films showing bilateral destructive lesions of the temporal bones, more extensive on the right side (September 23, 1946). *b*, Films taken ten months after completion of x-ray therapy to the temporal bone lesions. There is considerable filling in of the lesions with new bone (August 23, 1947).

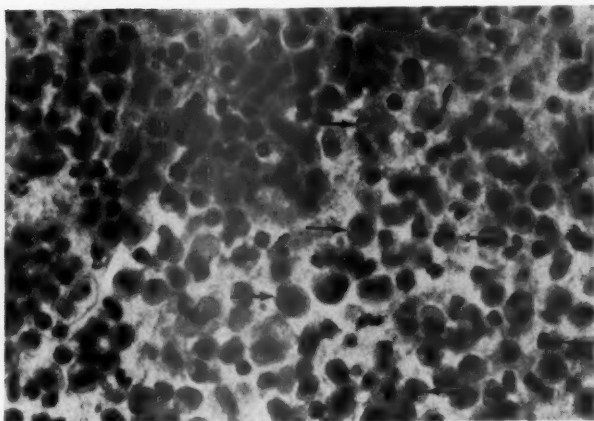


Fig. 5, Case 3.—Granulation tissue from the right external auditory canal. Histiocytes (—>) and eosinophiles (<—) are seen in great numbers.

was again hospitalized. It was noted that there was a yellowish clear discharge from the right ear and that the external canal was filled with a flaky, whitish yellow material. Sulfadiazine, Gm. 2, was given daily for four days while she was in the hospital. Sulfadiazine was continued in dosage of 2 grams daily for two weeks and then reduced to 1.5 grams daily for another two weeks.

*Examination:* She was first seen by us on September 5, 1946, six months after her initial complaints. At this time there was a yellowish serous discharge from the right ear and the external canal was filled with reddish grey granulation tissue. Culture from the ear grew streptococcus alpha and staphylococcus albus. The granulation tissue was removed under general anesthesia. The tympanic membrane appeared to be intact. Four days later the right external canal was again full of granulation tissue. The child was again given a general anesthetic and the granulation tissue removed from the ear a second time. At this time a very small fistula was found in the posterior wall of the external auditory canal 4 mm. from the annulus and extending into the mastoid cavity. X-ray films of the mastoid taken at this time revealed an extensive area of destruction of the right mastoid and the surrounding squamosal

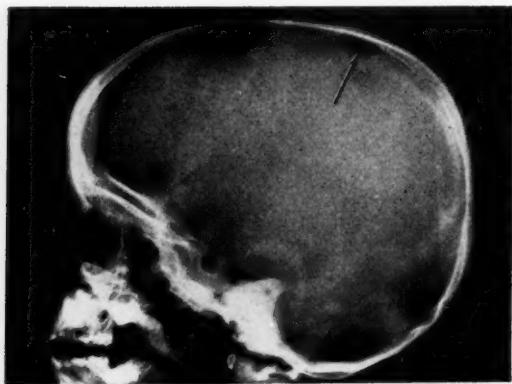


Fig. 6, Case 3.—A new lesion appeared in the skull one year after the temporal bone lesions were discovered (September 29, 1947).

portion of the temporal bone. The destruction involved the base of the pyramid. A similar process involved the left mastoid but was less extensive (Fig. 4a). There was also separation of the sutures of the skull. The chest film was essentially negative. X-ray films of the skeleton revealed no other lesions.

Neurological examination revealed a positive Macewen's sign and bilateral papilledema, more marked on the right. Spinal fluid pressure was recorded at 55 mm. of water. There were no cells and the Pandy test was negative.

Hematological studies showed normal numbers and normal appearing cells in the peripheral blood. Sternal marrow study revealed an increase in the mature eosinophilic elements. No lipoid-containing cells were seen.

*Histopathology:* The predominant cells in the tissue removed from the ear were histiocytes and eosinophiles. Some areas consisted predominantly of histiocytes with scattered eosinophiles. Other areas contained conspicuous accumulations of eosinophiles. A few mononuclear and several multinuclear giant cells were seen. A small region of necrosis contained moderate numbers of neutrophils. Occasional lymphocytes and neutrophils were scattered throughout the tissue (Fig. 5).

*Clinical Course:* Deep x-ray therapy was instituted immediately. The dosage to the temporal bones varied from 1450 r at the mastoid areas to 1400 r at the petrous apices given in 17 days. The technical factors were: P.K.V. 180; Filter 1 mm. Cu., 1 mm. Al; MA 20; HVL 1.3 mm. Cu; FSD 50 cm.; 35 r air per minute.

The right ear became dry in a week. Two months later Macewen's sign was negative, the papilledema was gone, and the child was clinically well.

One year later, the temporal bone lesions were filling in with new bone; however, a new osteolytic lesion was radiographically demonstrated near the vertex of the skull (Figs. 4b and 6). The child appeared clinically well. The new lesion was irradiated.

*Comment:* In this child of two the disease has expressed itself in a chronic, less severe form than in the previous two cases. The lesions involved both mastoids before any of the remaining skeleton. Discharge from the right ear began six months before we saw her and probably indicated the time when the lesion perforated the external auditory canal wall. In spite of this erosion, the mastoid and middle ear did not become infected. Diagnosis was made in this case by histological examination of the granulation tissue in the external auditory canal. Although it is realized that this small amount of tissue may not be entirely representative of the histological features of the lesion, it was adequate for diagnosis.

Some would feel that the diagnosis in this case should be eosinophilic granuloma because there was no evidence of visceral involvement and because of the granulomatous character of the lesion, having in it numerous histiocytes and eosinophiles but no foam cells. It can also be argued that this is Hand-Schüller-Christian disease in an early granulomatous phase before lipidization and collagenization of the lesions have taken place. A more serious diagnosis than eosinophilic granuloma seems justified because of the age of the patient and because multiple lesions have appeared. Only time will tell the degree of severity in which the disease will manifest itself. Prognosis must necessarily be guarded.

Lederer's case<sup>31</sup> occurred in a two-year-old child. The mastoid as well as several other areas of the skull were involved. Diagnosis was made by biopsy of a lesion of the frontal bone and from granulation tissue in the external auditory canal, thus mastoidectomy was prevented. In Shea's case<sup>28</sup> the lesions involved a femur and the temporal bone. The lesion of the femur responded to x-ray therapy and so it was subsequently applied to the mastoid with equally good

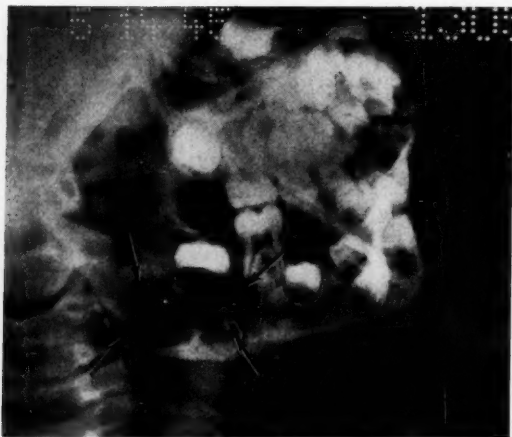


Fig. 7, Case 5.—Eosinophilic granuloma of the mandible (May 14, 1945).

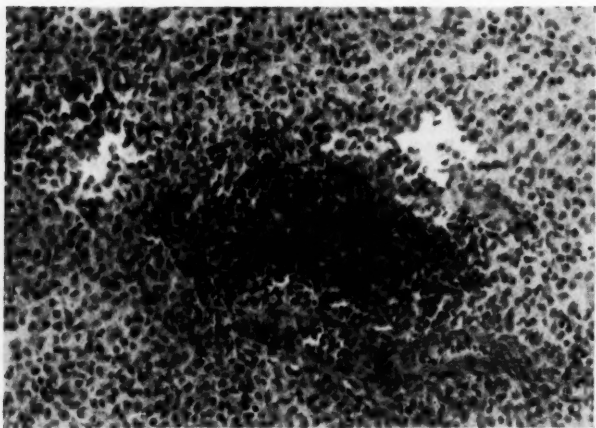


Fig. 8, Case 5.—Tissue removed from the mandible. There is a dense accumulation of mononuclear and polymorphonuclear eosinophiles surrounded by a zone containing predominantly histiocytes.

results. Thus a therapeutic test indicated the probable diagnosis and mastoidectomy was prevented.

Rosenberger<sup>35</sup> also made the diagnosis in a case by histological examination of granulation tissue in the external auditory canal.

Curtis and Cawley<sup>36</sup> noted the disease in an eight-month-old infant in which there were lesions of the right mastoid, left ilium, and second right rib as well as cutaneous eruptions, which they termed eosinophilic granuloma with cutaneous manifestations. The eruption first resembled that of seborrheic dermatitis and then developed into small red, discrete, coalescent papules on the buttocks and genitalia and erythematous eroded patches in the mouth. Later the abdomen, axillae, inguinal and perianal regions become involved. Biopsy of the skin lesions revealed many histiocytes and in some areas groups of eosinophiles. Following x-ray therapy there was complete healing of all lesions. It would appear that in the case of an infant with such widespread involvement the diagnosis of eosinophilic granuloma must be used reservedly.

CASE 4.—R. B., age 11.

*History:* On January 1, 1940, this 11-year-old boy developed a head cold and a generalized headache. Also at this time he noted a tender area over the outer aspect of the left eyebrow. Mild malaise and nasal discharge continued during the following week. The mother stated that the patient also had a fever as high as 103° F. on one occasion. During the following month the tenderness and swelling over the left eye persisted. There were occasional sharp stinging pains and at night a dull ache in that region.

*Examination:* On February 5, when he was first examined, there was slight swelling and marked tenderness over the lateral aspect of the left supraorbital ridge. Temperature and blood counts were normal. X-ray films revealed an osteolytic area measuring 2 x 1 cm. over the lateral margin of the left supraorbital ridge (Fig. 9).

*Operation:* On February 6 a partial osteotomy was performed by Dr. D. B. Phemister. The lateral margin of the left supraorbital ridge was exposed, revealing a mass of granulation tissue bulging up beneath the periosteum through a defect in the outer table of the skull. After all granulations were removed, a small communication with the left frontal sinus was detected. Culture from this tissue grew staphylococcus aureus hemolyticus.



Fig. 9, Case 4.—Eosinophilic granuloma of the left frontal bone at the lateral aspect of the supraorbital ridge (February 6, 1940).

Fig. 10, Case 6.—A lesion involving the roof of the right orbit resulted in proptosis, downward displacement of the eye and drooping of the upper eyelid (April 29, 1942).



Fig. 11, Case 6.—The osteolytic lesion is seen to involve the lateral aspect of the right supraorbital ridge and the roof of the orbit (April 27, 1942).



*Histopathology:* The striking feature was large numbers of histiocytes occurring in sheets and irregularly arranged strands along fibrous connective tissue septa. Eosinophiles were scattered throughout in large numbers and in some areas in accumulations. Smaller numbers of neutrophils, lymphocytes, erythrocytes, and multinucleated and mononucleated giant cells were present.

*Clinical Course:* Recovery from the operation was uneventful. When last seen on March 12, 1941 (13 months after surgery), the patient was clinically well and x-ray films demonstrated filling in of the bony defect. There were no new lesions.

*Diagnosis:* Eosinophilic granuloma.

*Comment:* The lateral supraorbital region of the frontal bone and the roof of the orbit seems to be a region of predilection for the occurrence of eosinophilic granuloma. This is readily appreciated when reviewing case reports appearing in the literature.<sup>23, 37-40</sup>

CASE 5.—R. T., age 6.

*History:* For about six weeks this six-year-old boy had noticed a lump at the angle of his jaw on the left side. There was no pain or illness at any time. The mass gradually increased in size. There was no history of trauma.

*Examination:* When he was first seen on March 3, 1945, there was a firm, slightly tender, round mass at the angle of the jaw on the left side. It was fixed and seemed continuous with the bone of the mandible. Peripheral blood counts were normal. Tuberculin test (1:1000) and Kahn test were negative.

X-ray films revealed an osteolytic lesion measuring 1.5 x 3 cm. and occupying the arch and angle of the mandible on the left side (Fig. 7).

*Operation:* On March 19, 1945, the lesion was biopsied and curetted by Dr. D. B. Phemister. The lateral aspect of the mandible was exposed, revealing bulging and thinning of the cortex. The bone lesion beneath this was filled with a greyish yellow, friable tissue. Frozen section revealed it to be an eosinophilic granuloma. The lesion extended into the fibers of origin of the masseter muscle. Tight closure of the soft tissues was made.

*Histopathology:* There was a vascular, extremely cellular, granulation-like tissue which was diffusely and focally infiltrated with eosinophilic polymorphonuclear leukocytes. The other most prominent cell type was a medium-sized round cell with a medium

to large pale nucleus (histiocyte). There were multinucleated giant cells in several areas. The connective tissue stroma was scanty (Fig. 8).

*Clinical Course:* The postoperative course was uneventful. X-ray films taken two months postoperatively revealed that the bony defect of the mandible was filling in. Two and one-half years later the patient was clinically well.

*Diagnosis:* Eosinophilic granuloma.

*Comment:* Salman and Darlington<sup>41</sup> report a case in which there was a solitary lesion in the mandible with marked mobility of the teeth.

Surgical removal of an eosinophilic granuloma is followed by healing. If surgical removal is not easily accomplished or if there appears to be danger of fracture if complete removal is attempted, the preferred treatment should be biopsy diagnosis followed by x-ray therapy.

CASE 6.—R. W., age 31.

When first seen on April 22, 1942, this 31-year-old male stated that for one year he had noted gradually increasing bulging of the right eye and inability to open the eye as widely as the other (Fig. 10).

*Examination:* There was 5 mm. proptosis of the right eye. The right palpebral fissure measured 7 mm. as compared to 8.5 mm. on the left. There was limitation of movement of the right globe on looking to the right and upward. There was weakness of the right palpebral muscle. The globe was displaced downward by a soft tender mass which could be felt beneath the supraorbital ridge. There was no fever, and peripheral blood studies were normal. Blood cholesterol: total 76.4 mg. per 100 cc. (F-62.0, esters—14.4) X-ray films demonstrated an osteolytic lesion involving the right supraorbital ridge and extending posteriorly along the roof of the orbit (Fig. 11).

*Operation:* An incision was made through the eyebrow. A mass covered by a thin shell of bone protruded downward from the roof of the orbit. The mass consisted of a thin granulation tissue wall with a large central cystic area. It contained a thick chocolate-colored material having in it semi-solid yellowish particles. The

dura was exposed when the walls of the cyst were curetted away. Three grams of sulfanilamide and a small drain were placed in the cavity and the wound closed with interrupted silk sutures. Recovery was uneventful.

*Histopathology:* The cyst wall consisted of a layer of fibrous granulation tissue. Some areas consisted only of very dense collagenous fibrous tissue containing scattered hemosiderin crystals. In other regions were interlacing strands of fibrous connective tissue separated by groups of lymphocytes, a few small blood vessels, areas of hemorrhage, scattered hemosiderin crystals, and cholesterol clefts. Many multinucleated giant cells were found in these areas. More peripherally and adjacent to the bony wall of the lesion were moderate numbers of foam cells. No eosinophiles were present (Fig. 12a and b).

*Clinical Course:* Recovery was uneventful. Six years later x-ray films demonstrated no new lesions in the skull. The defect from the old frontal bone lesion showed little change from the immediate postoperative appearance.

*Comment:* Symptoms from the lesion in this case had been present for one year. The age of the lesion was reflected in the histopathological picture in the form of scarring, lipidization, and central necrosis. The case fits the clinical picture of eosinophilic granuloma; however, there were no eosinophiles in the lesion.

The exact nature of such cystic granulomatous lesions of the frontal bone remains obscure. In 1941 Lillie and Pastore<sup>42</sup> reported two cases almost identical to ours. Both of their patients also had an osteolytic lesion of the frontal bone and roof of the orbit which was found to be cystic at time of operation. In both cases there was proptosis of several months' duration and one or more short attacks of severe pain in the frontal region. Tissue removed in their cases showed chronic inflammatory granulation tissue with cholesterol clefts and calcium deposits. Simonton recently reported a similar case. This type of lesion occurs characteristically in the bone of the roof of the orbit and adjacent supraorbital ridge. It is quiescent until hemorrhage occurs into the lesion with resulting pain or until the orbit is invaded and proptosis becomes evident. The histopathology offers no significant clue as to the etiology of this lesion. We know that this particular region of the frontal bone is a site of predilection for eosinophilic granuloma. It may be that these lesions represent eosinophilic granuloma in a phase of central degeneration, hemorrhage and scarring.

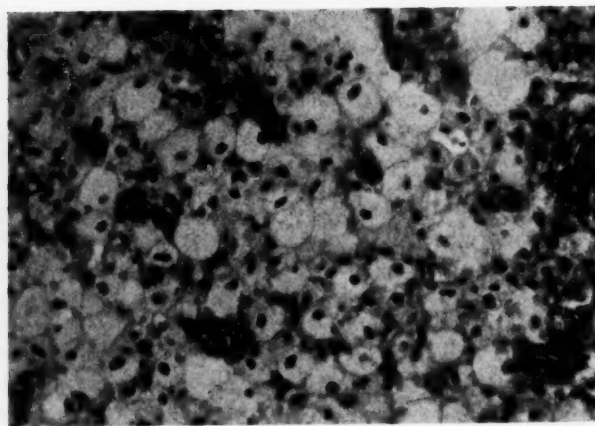
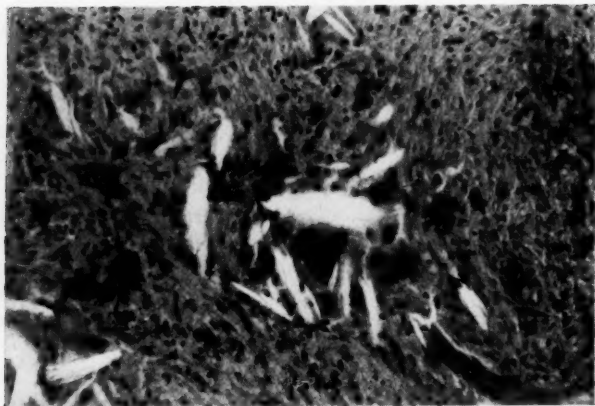


Fig. 12, Case 6.—*a*, Some areas of the wall of the cystic lesion consisted of fibrous granulation tissue containing blood pigment, cholesterol clefts, areas of hemorrhage, blood vessels, multinuclear giant cells, lymphocytes and a few histiocytes. *b*, Other areas of the cyst wall contained many foam cells.

## CASE 7.—G. F., age 47.

*History:* This 47-year-old male was first seen on November 26, 1947. He stated that for the previous four weeks he had a continual right frontal headache gradually increasing in severity. Aspirin and codeine gave no relief.

*Examination:* Physical examination was negative except for slight tenderness over the right temporal region. It was thought that this might be a right temporal arteritis. Skull films were reported to be negative on November 28, 1947 (Fig. 13a). Chest film was negative.

*Clinical Course:* Severe pain continued day and night unrelied by local heat applications or codeine. Skull films taken on December 13, 1947, revealed an area of decreased density measuring 1.4 cm. in diameter in the lateral aspect of the right frontal bone. There was a central mottled area in which near normal bone density was retained (Fig. 13b). Examination in retrospect of the skull films taken 15 days previously revealed that the lesion was barely discernible.

*Operation:* On December 23, 1947, Dr. J. Harvey removed the diseased bone surgically. Beneath a thinned outer table was soft, dark grey granulation tissue. A sequestrum was not found. Frozen section revealed this to be an eosinophilic granuloma.

The postoperative course was uneventful. The patient has had no further frontal pain.

*Histopathology:* In some areas there was a loose fibrous connective tissue stroma containing large numbers of histiocytes and eosinophiles. Many multinucleated giant cells were present in these active areas. Other regions consisted of more dense fibrous tissue.

*Diagnosis:* Eosinophilic granuloma.

*Comment:* Constant severe pain such as occurred in this case is unusual in eosinophilic granuloma. The pain may have been due to the fact that the lesion developed so rapidly. Another interesting feature is the x-ray appearance of a sequestrum in the lesion. A sequestrum was not found at operation. It seems probable that this was not a true sequestrum but that this appearance was due to the lesion assuming a doughnut shape which left a less diseased central portion of bone.

In making the differential diagnosis the following should be borne in mind:



Fig. 13. Case 7.—*a*, Skull films originally thought to be negative but when examined in retrospect a barely discernible lesion is seen in the temporal region (November 28, 1947). *b*, Fifteen days later the lesion is well seen and contains a central area of near normal bone density (December 13, 1947).

The individual bone lesions in Hand-Schüller-Christian disease and eosinophilic granuloma appear identical on x-ray examination. Hand-Schüller-Christian disease is characterized by multiple lesions. In eosinophilic granuloma there are one or a few lesions. Visceral, neural, and cutaneous lesions occur commonly in Hand-Schüller-Christian disease. It seems preferable to consider eosinophilic granuloma as a milder form without extraskeletal lesions.

**Metastatic Osteolytic Malignant Tumor.** Skull metastases usually appear as numerous small lesions. Single large osteolytic lesions do occur, however. The borders are sharply circumscribed and may assume a polyarcuate or amoeboid form. Primary lesions should be particularly sought for in the thyroid and the breast. The metastatic skull lesions of Ewing's sarcoma can often be differentiated by the presence in them of areas of bone proliferation. Pain is common to metastatic lesions, whereas in the Hand-Schüller-Christian group the skeletal lesions are often silent. Malignant tumors usually occur in an older age group.

**Primary Carcinoma.** The osteolytic lesion seen in primary carcinoma of the middle ear and mastoid may be differentiated by the history of chronic suppuration, and the presence of severe pain, bleeding and ulceration. Biopsy from the ear canal makes the diagnosis of carcinoma. The labyrinthine capsule is rather resistant to invasion by carcinoma<sup>43</sup> which is not true of the lesions of Hand-Schüller-Christian disease.

**Secondary Cholesteatoma.** The bone defect is usually small and occupies the region of the mastoid antrum. It does not involve the squamosal portion of the temporal bone as frequently happens in Hand-Schüller-Christian disease. The history of chronic suppuration and the finding of a defect in the tympanic membrane which may contain flaky cholesteatomatous material aid in identifying this condition.

**Primary Cholesteatoma (Epidermoid tumors).** These pearly tumors may involve any part of the skull but most often the temporal bone. They may exist for years while gradually increasing in size. The lesion is seen on x-ray examination to have a bordering zone of osteosclerosis. Sometimes a fluctuant mass may be felt surrounded by a bony ridge.

**Osteomyelitis.** The spreading type of osteomyelitis of the skull usually offers no great problem in differential diagnosis. Localized types, particularly when due to metastatic hematogenous spread, may closely simulate eosinophilic granuloma both clinically and radio-



graphically. Pain and sequestration favor the diagnosis of osteomyelitis; however, a very active eosinophilic granuloma may produce this identical picture.

**Multiple Myeloma.** The osteolytic lesions are generally smaller and more numerous than in Hand-Schüller-Christian disease. The ribs are often extensively involved. Nearly all cases occur in persons past the age of 40. Bence-Jones albuminuria is present in about half the cases.

**Congenital Skull Dehiscences.** The most common type is persisting parietal foramina. They are usually but not necessarily bilateral and occur parasagittally just anterior to the lambdoidal suture.

**Tuberculosis.** Circumscribed tuberculosis of the flat bones of the skull produces a punched out area of bone destruction. It occurs in early childhood and usually antecedent lesions are found in the lungs, lymph nodes or other bones of the skeleton.

**Syphilis.** The skull lesions are usually limited to the frontal and parietal regions. The early porous bone lesions may coalesce to form larger serpiginous defects. The clinical findings and serologic tests make the diagnosis.

**Fungus Lesions.** Skull lesions may occur in actinomycosis, blastomycosis and coccidiomycosis. The lesions are characteristically painless and develop slowly. Because of their low virulence a bordering zone of bone proliferation is often seen. Identification of the specific fungi is made by biopsy of the skull lesion or lesions elsewhere in the body.

#### SUMMARY AND CONCLUSIONS

The temporal bone may be the site of early lesions in Hand-Schüller-Christian disease. When small, these temporal bone lesions are silent. As the lesion grows in size, it may manifest itself in several ways: by perforation of the external auditory canal wall; erosion through the cortex of the mastoid, zygomatic and squamosal portions of the temporal bone; invasion of the labyrinthine capsule; involvement of the facial nerve; encroachment upon structures in the jugular foramen; secondary infection. Worthy of reiteration is the fact that when exuberant xanthomatous granulations invade the external auditory canal, they do so by passing through the canal wall and not through a defect in the tympanic membrane. In the absence of other pathology the tympanic membrane remains intact. When granulations appear in the external auditory canal, the diagnosis can usually be made by microscopic examination of this tissue.

Extremely significant is the fact that uncomplicated lesions of Hand-Schüller-Christian disease or eosinophilic granuloma of the temporal bone are almost always painless.

Secondary infection frequently occurs in such a diseased temporal bone. This may occur via the eustachian tube following an upper respiratory infection or through a fistulous tract in the external auditory canal wall. When this happens the primary disease process is often overlooked. An important clue is the radiographic evidence of bone destruction out of all proportion to that which one would expect from the duration and degree of infection. When the nature of the lesion is suspected, it is important to seek radiographic evidence of other skeletal or visceral lesions.

Mastoidectomy must sometimes be performed in the event of a complicating infection. The operation should be followed by x-ray therapy to the area. These mastoid cavities heal slowly unless such irradiation is given.

Positive biopsy diagnosis of eosinophilic granuloma or Hand-Schüller-Christian disease must be made before irradiation is given.

Eosinophilic granuloma is a milder form of the same basic disorder underlying Hand-Schüller-Christian disease. It usually manifests itself by a single bone lesion; however, several may occur. Usually pain is minimal in eosinophilic granuloma. In rapidly developing lesions pain may be constant and severe.

The lateral supraorbital region of the frontal bone and adjacent roof of the orbit appears to be a site of predilection for these solitary granulomas. Certain chocolate-colored cysts with chronic granulation tissue walls are found in this area. They may represent a chronic degenerating stage of eosinophilic granuloma.

Either surgical removal or irradiation of an eosinophilic granuloma results in a cure of that lesion. Because it is necessary to establish the diagnosis by biopsy, it is common procedure to remove the entire lesion at time of surgery. When other lesions exist or subsequent lesions occur, they can be treated by irradiation.

950 EAST 59TH STREET.

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ASSOCIATED SYMPTOMATOLOGY OF DISEASES OF  
THE EPIPHARYNX

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Symptomatology in relation to the epipharynx has been a challenge to the acumen and thoroughness of the otolaryngologist since the days of Thornwaldt,<sup>1</sup> when he first published his monograph "Bursa Pharyngea" in 1885. Despite earlier publications and many recent articles on the nasopharynx, the importance of the subject is apt to be more or less neglected. Too often in routine examination a critical survey of the epipharynx is omitted or considered of little importance in patients with postnasal discharge, recurrent pharyngitis, cough, headache, persistent fever, bleeding, hoarseness or asthma. In many instances the onset of recurring rhinitis (frequent colds) has its origin in the vault of the epipharynx (nasopharyngitis). The patient often states, "I have a burning sensation back of my palate." Deafness due to tubal insufficiency from lymphoid hyperplasia throughout the vault is to be included in this group. Much of the recent literature is directed mainly to the subject from the standpoint of diagnosis and treatment of tubal obstruction and various forms of hearing impairment by irradiation.

It is the purpose of this report to present a study of 150 cases observed over a period of two years, from the standpoint of a wide variety of symptoms and complaints, which have their source solely in the epipharynx. It must be borne in mind that this group of patients was studied carefully to eliminate all other factors which might produce the symptoms referred to, such as accessory sinus disease, hyperplastic turbinal changes, cancer, or systemic disorders. For example, if a sinus condition producing postnasal discharge were present, the case was not included in this study. Even though a pathological condition of the epipharynx was found, it was assumed that this condition was secondary to disease in the nose and, therefore, the case was not included in this analysis.

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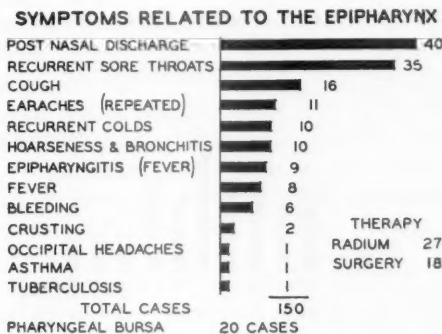
Presented before the American Laryngological Association, Hot Springs, Va., April 14, 1948.

A number of patients, in whom evidence of an allergic disturbance was noted in either the history or upon examination, were not considered in this report. For a similar reason, patients complaining of that present-day, popular, and much abused term, "postnasal drip," where the discomfort and irritation is self-inflicted due to the habit of hawking or rasping, likewise are not included, since no gross pathology was present in the epipharynx. This is the same group in which responses from such a symptom varied from that of apprehension or an esthetic annoyance to the extreme of psychologic upheaval.

The age of the patients studied in this group ranged from 5 to 75 years, with the greatest number, 16.6 per cent, between the ages of 40 and 45. There were 58 males and 92 females. The most frequent complaint was postnasal discharge, thickened in consistency, and yellowish in color, sometimes foul in taste and occasionally noted as a mucoid, inspissated clump in the mesopharynx. The latter is often indicative of a true pharyngeal bursa. Next in order of frequency was the history of repeated sore throats or chronic pharyngitis in which cervical adenitis was sometimes present, accompanied by low-grade temperature. The occasional sore throat which appears in the morning and subsides during the day is an example of the typical description given by the patient. Frequently, one symptom may be intimately related to another, occurring in association, but the immediate complaint is the one recorded in this classification. This is illustrated in patients in whom the cardinal complaint is postnasal discharge, while the associated history might include sore throat or cough or hoarseness.

Ten patients complained of frequent colds which seemed to have had their origin in the epipharynx, the history of onset being described as a burning sensation above the palate. There were nine cases of epipharyngitis with fever. Bleeding, in the form of bloody expectoration or cough, was observed in six cases. Three of these patients were suspected of having pulmonary tuberculosis and two of them had received sanitarium care, although no acid-fast bacilli had been discovered. One case of postnasal hemorrhage was severe enough to have previously required postnasal packing and one blood transfusion. The bleeding point was discovered by direct nasopharyngeal examination. Bleeding granulation tissue was found in the midline of the vault. Histologic study was negative for a neoplasm. This patient was treated by means of electrocautery employed locally, supplemented with rutin and ascorbic acid parenterally. In a recent recheck after a period of eight months, the





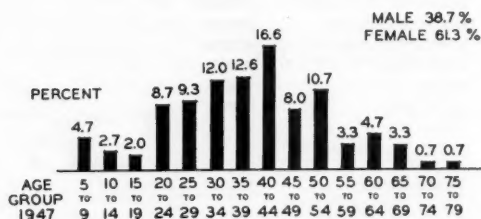
nasal vault appears smooth and there has been no recurrence of the bleeding episode.

One patient, suspected of pulmonary tuberculosis because of blood-stained sputum, had a small, bloody area of granulation tissue in the vault. Bronchoscopy had been performed and all secretions were reported negative. She had a positive Rumpel-Leede test, indicating increased capillary fragility, suggesting a probable vitamin C deficiency because she never had eaten citrus fruits. Silver nitrate (5%) applied locally was supplemented by large doses of ascorbic acid. She now has bloody sputum at infrequent intervals and then only following a cold; the bleeding apparently comes from the epipharynx.

In 16 patients in this series, cough was a major symptom—nonproductive and paroxysmal in character—sometimes described as a “tickling sensation” and not relieved by the usual sedatives. Lymphoid hyperplasia with hyperemic and thickened lateral bands behind the posterior pillars was the predominant finding in these patients. There was prompt relief following local treatment to this area. Hoarseness or laryngitis was present in 10 cases, in each secondary to postnasal discharge. There were 10 cases in which there was a history of frequent colds which apparently had their origin in the nasopharynx. It is my belief that many of our so-called head colds begin as an epipharyngitis.

Epipharyngitis, referred to as a soreness back of the palate or a burning sensation in this area, and accompanied by slight fever, was observed in nine cases. Asthma was relieved in one patient in

PERCENTAGE DISTRIBUTION BY AGE GROUP  
OF 150 CASES WITH PATHOLOGY OF THE EPIPHARYNX  
IN RELATION TO SYMPTOMATOLOGY



whom all other forms of treatment, including allergenic therapy, had failed. A large, bulging, closed pharyngeal bursa, with a pin-point opening allowing the escape of purulent secretion, was discovered. In a similar case of a closed bursa with a bulging vault, the patient complained of impaired nasal breathing. The sac contained a thickened, jelly-like mucus. Removal of the sac gave complete relief of symptoms in both instances.

Intermittent otalgia with fullness and hearing impairment was the primary complaint in 11 cases. With the exception of two adults, these were all children under 16 years of age. Tonsils and adenoids had been previously removed. The tympanic membrane picture was varied, but gave evidence of serous exudate or inflammation. In a few of the cases myringotomy and inflation with recovery of fluid confirmed the ear findings. The presence of massive lymphoid tissue or adenoid growth in the children required surgery or radium, or both.

It is noteworthy that in eight of the reported cases, there was a history of persistent fever for a period of five months or more, and in one case, of 18 months' duration. The temperature ranged from 99 to 100° F. Three of these patients were given the benefit of surgery, while the others were treated conservatively. The systemic symptoms were constant fatigue, neuralgia or arthralgia, and sometimes a loss of weight was reported. The diagnosis was based upon the fact that no specific or local cause other than the epipharyngeal pathology could be found to account for the fever. All of the patients were studied exhaustively by an internist for the cause of obscure fever. It should be stated that following the first examination, which required slight manipulation of the infected epi-

pharyngeal tissue, such as probing, a flare-up of the temperature or exacerbation of the systemic symptoms sometimes occurred. Occasionally cervical adenitis was observed to have followed such a procedure. It is also significant that in this particular group the sedimentation rate and white cell count were only slightly elevated, if at all. Furthermore, sulfonamide and penicillin therapy had been administered without any influence upon the course of the temperature. Final diagnosis was definitely established when the temperature returned to normal and the symptoms disappeared following treatment of the infected epipharyngeal tissue. In this connection, I should like to emphasize the importance of a thorough study of the epipharynx in all individuals who have a low-grade fever of unknown origin.

One case of tuberculosis of the nasopharynx is reported, not as a symptom *per se* of the disease, however, because pulmonary involvement was a known factor. The so-called "postnasal drip" complaint led to the diagnosis of the primary source. This patient had a superficial ulcerating lesion, ovoid in shape, in the vault of the epipharynx, covered with a grayish exudate. Tubercle bacilli were recovered by smear examination. It is advisable, therefore, to bear in mind investigation of the epipharynx in cases of pulmonary tuberculosis. The healing effects of streptomycin in tuberculous lesions of the larynx and oropharynx have been dramatic. Its application to lesions of the nasopharynx have been reported as equally effective.

One patient with the cardinal complaint of occipital headaches is reported. In contrast to sphenoidal headaches, which are more generalized over the occiput, the pain is more localized. The diagnosis was based upon the presence of a deep median crypt and relief of the headaches which followed conservative treatment. In such instances there is believed to be an extension of the notochord remnant upward and backward against the basilar portion of the occipital bone. It may even penetrate the basilar fibrocartilage. Such extension is to be suspected in occipital headaches, as emphasized by Kully,<sup>8</sup> who reported 12 similar cases in 1934.

Crusting was present in two cases. The mucous membrane was smooth and dry. A shallow bursa with a large opening was observed, with crusts adherent to the lower lip of the sac.

The presence of a bursa does not necessarily mean that it is pathologic. Its presence has been noted without clinical symptoms. To be pathologic the sac must become infected. This is apt to ensue

from trauma, such as may occur in scraping of adenoid tissue. It is therefore possible to find a pharyngeal bursa after removal of adenoids. The incomplete removal or the presence of adenoid remnants is a frequent cause of lymphoid hypertrophy and subsequent formation of retention cysts or abscess or chronic inflammation. During the period of involution of adenoid tissue, cysts or abscesses may develop within any of the adenoid clefts, more often in the median recess. They may, therefore, be considered as congenital or acquired.

One should be constantly alert to the possibility of malignant growths in the nasopharynx. There is none reported in this series. In one case, however, the first evidence of a cancer was discovered through biopsy of an enlarged cervical lymph node. This clue led to the nasopharyngeal examination from which diagnosis of anaplastic carcinoma was confirmed. These cancers, Williams states, occur most commonly between the ages of 40 and 60. The most frequent type encountered is highly malignant squamous-cell carcinoma. In 40 per cent of the cases reported by Nielsen,<sup>6</sup> cervical gland enlargement was the first symptom observed.

Diseases of the nose and sinuses and allergy must be eliminated before all evidence can be placed against the nasopharynx as a primary focus. The history alone is often indicative of the diagnosis. The sudden appearance of a mucoid clump into the mouth is the typical description given by the patient when a pouch is present. Inspection may be accomplished by use of the nasopharyngoscope, posterior rhinoscopy with the Michel mirror, by anterior rhinoscopy, or by direct nasopharyngoscopy. The last-named method is best accomplished by means of a palate retractor or the Yankauer speculum. This, to me, is the instrument of choice, and most serviceable because it provides a direct view of the vault and allows for instrumentation. Probing with a cotton-tipped applicator will reveal the depth and limitations of a pouch, as well as the overgrowth of lymphoid tissue. When the mere touch of an applicator provokes bleeding, it is evidence that inflammation or granulation tissue is present. In many instances the epipharynx is revealed by rhinoscopic inspection. When the turbinates are shrunken and the septum is not obstructive, it is easy to observe the vault through one side of the nose while probing this field through the other side with a small cotton-tipped applicator. For the study of neoplasms, choanal fibromas or polyps, the mirror gives adequate exposure. For lesions around the eustachian tube orifice and in and about Rosenmüller's fossa, the nasopharyngoscope is the most serviceable.

The bacteriologic study of the epipharynx was not particularly informative except in those cases of persistent fever. The predominant organisms recovered by culture were nonhemolytic streptococcus, streptococcus viridans, hemolytic staphylococcus aureus, and diphtheroids. In the patients with fever, however, hemolytic streptococcus was the predominant organism, while in persons with closed bursas, cultures often proved sterile.

In this series of cases, diagnosed and treated, examination of the postnasal space revealed a wide variety of findings. The pharyngeal bursa has an opening into the sac which varies in size from that of a pin point to a vertical slit, or a large elliptical opening. It may give the impression of a mere cul-de-sac. The bursa pharyngea is not a closed sac lined with endothelium, nor is it of mesodermic origin. Therefore, in the strictest sense it is not a true bursa, and only long-continued use of the term has justified this terminology. Sometimes the opening has completely closed, forming a retention cyst or an abscess. The content may be purulent, cystic in character, or a jelly-like mucus. When infected, the walls are reddened and there may be lymphoid tissue or granulation tissue within the sac.

The more common type encountered is the lymphoid hypertrophy which occurs as a result of repeated inflammation, and thereby forms pockets, linear furrows or retention cysts. The contents of the cyst may be purulent, thus it is frequently termed an abscess. The hypertrophy may be sufficient to be termed an adenoid growth. In some cases there is merely an infected median recess. Thus no constant finding in the epipharynx is typical of one particular symptom or another. They are all intimately related, and the significance of findings should be given conscientious evaluation as to the cause of symptoms.

Histologic studies carried out in a number of the cases reported consistently reveal chronic inflammation, and at no time did we find normal respiratory epithelium. The surface covering showed transitional epithelium with squamous metaplasia, and the stroma gave evidence of chronic inflammation by the presence of round cell infiltration and proliferation of fibroblasts. Some sections evidenced greater round cell infiltration than others, indicative of more intense chronic inflammation.

Treatment in these cases consisted of surgery, irradiation and local therapy. In treating the nasopharynx, surgical removal of hypertrophied lymphoid tissue, if present, is indicated. In the cases reported, radium was employed in addition to surgery, because we

were concerned with a regrowth of lymphoid tissue following previous adenoidectomy.

Local treatment consisted of the application of 5% silver nitrate through the Yankauer speculum. It is possible at times to make this application with the aid of a rhinoscope when space permits. The use of a small cotton-tipped applicator is recommended so as to avoid an excessive amount of solution which might run down into the pharynx. More intensive caustic materials are not advised because of probable subsequent destruction of mucus glands or possible scar tissue formation. However, electrocauterization was employed in two cases in which bleeding was the most prominent symptom, and trichloroacetic acid was applied in two others of this series.

Radium was applied in those cases in which the condition did not respond to conservative local management. The manner of application is essentially the Crowe technique, using the 50 mg. monel metal radium applicator at intervals of one month for two and sometimes three treatments. The duration of the exposure is 15 minutes. A note of caution should be sounded concerning the indiscriminate use of radium for treatment to the epipharynx. One should inquire always as to whether or not the patient has had previous radium therapy. Certainly, it should not be applied when no discernible pathological condition is present in the nasopharynx, nor should it be employed solely on the basis of ear findings. It is evident that young lymphoid tissue responds to irradiation far better than adult tissue. Furthermore, lymphoid tissue can regenerate following such therapy, and it is possible to have metaplastic changes take place. How are we to know in what percentage of cases the stimulating effects may bring about neoplastic formation in years to come? These are questions which concern us for the future, and further observations and studies are necessary before we can evaluate the true permanent effects of irradiation therapy.

#### SUMMARY

1. A review of 150 cases of epipharyngeal pathological conditions in the order of frequency of associated symptoms is presented.
2. In 40 cases the most prominent symptom was postnasal discharge. Next in order of frequency was recurrent sore throat which occurred in 35 cases. The other conditions presented in order of frequency were: cough, earache, recurrent colds, hoarseness and bronchitis, epipharyngitis, fever, bleeding, crusting, and one case each in occipital headache, asthma and tuberculosis.

3. It is the intent of this paper to point out that more attention should be directed to routine examination of the epipharynx, particularly when dealing with symptoms referred to in this discussion.

307 NORTH MICHIGAN AVENUE.

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LVIII

REPORT OF POSTOPERATIVE COURSE OF SUBPERI-  
CHONDRAL TOTAL LARYNGECTOMIES

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AND

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In 1938 Crowe and Broyles published the details of a one-stage operation for total laryngectomy in selected cases of cancer of the larynx. This technique was carefully planned so as to preserve as much as possible of the undiseased structural elements of the neck and to provide the best possible closure of the pharyngeal defect resulting from removal of the larynx.

These authors emphasized that the cases suitable for this type of operation are only those in which the cancer has not invaded the cartilages, false cords, or ventricles, arytenoids or epiglottis, and has not extended into the muscles or glands of the neck.

A number of patients have been operated upon with this technique, and it now seems advisable to review the results obtained, especially with regard to the postoperative course of the patients. Some modifications in technique of the original operation are also discussed.

It is important previous to operation to have a thorough medical check-up and to remove any foci of infection in the upper air passages, especially in the teeth and gums.

The preliminary stages of the operation can be performed under local anesthesia. During actual removal of the larynx, the patient is anesthetized with pentothal sodium.

The operative procedure used at present differs from the original in making use of the mucous membrane on the dorsal part of the epiglottis to obtain a complete mucous membrane closure of the

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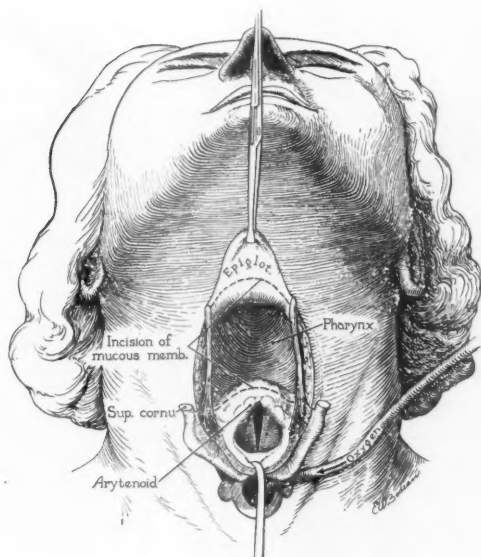


Fig. 1.—Incision into pharynx through thyro-hyoid membrane.

pharyngeal defect and the use of chemotherapy. An outline of the stages of the operation follows.

The patient is placed on the operating table in a moderate Trendelenburg position. The head is extended as much as possible. A sandbag under the shoulders may be necessary to obtain sufficient extension. After local infiltration of the skin and the deep tissues of the front of the neck with procaine, a midline incision is made from the hyoid to about one centimeter above the sternum. The strap muscles are separated and the isthmus of the thyroid divided. At this point, the patient is anesthetized with pentothal sodium. The inner tracheotomy tube is then inserted into the trachea below the second ring and oxygen insufflated. The perichondrium is elevated from the thyroid cartilage, the larynx retracted and the cornua of the thyroid cartilage divided. The thyrohyoid membrane is then incised.

The changes in this stage of the operation are shown in Figs. 1-3. The incision through the thyrohyoid membrane into the pharynx in the present technique is made directly through the base of the epiglottis leaving this structure attached to the tongue. In the original description of the operation, the opening into the

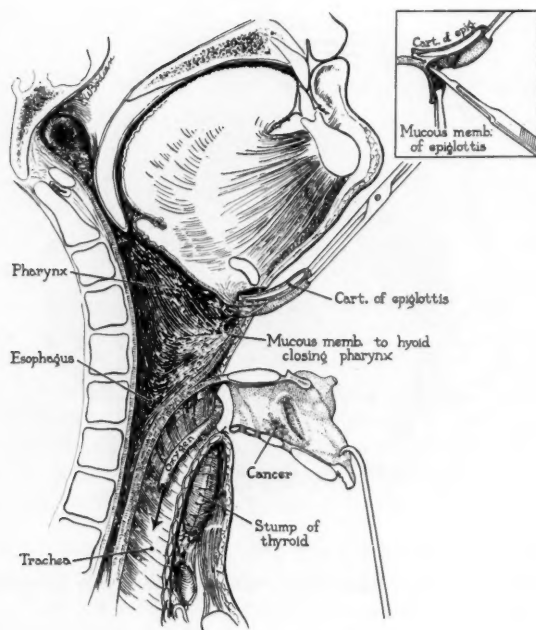


Fig. 2.—Removal of larynx and epiglottis.

pharynx was made between the epiglottis and the base of the tongue. We feel that leaving the epiglottis attached to the tongue at this stage in the operation is more advantageous for several reasons. First, a better view into the pharynx can be maintained during the operation; and second, the mucous membrane on the dorsal surface of the epiglottis can be utilized later in closing the pharyngeal defect.

Under direct vision, the inferior constrictors are now freed from the larynx on each side, and the incision in the thyrohyoid membrane extended down and across the posterior face of the cricoid. The larynx is then freed from the esophagus and removed. The stump of the trachea is anchored to the sternohyoid muscles. The mucous membrane on the upper surface of the epiglottis is incised and elevated and the epiglottis removed. The mucous membrane from the posterior face of the cricoid is then sutured to the mucous membrane from the upper surface of the epiglottis and anchored to connective tissue at the upper angle of the wound. The remaining

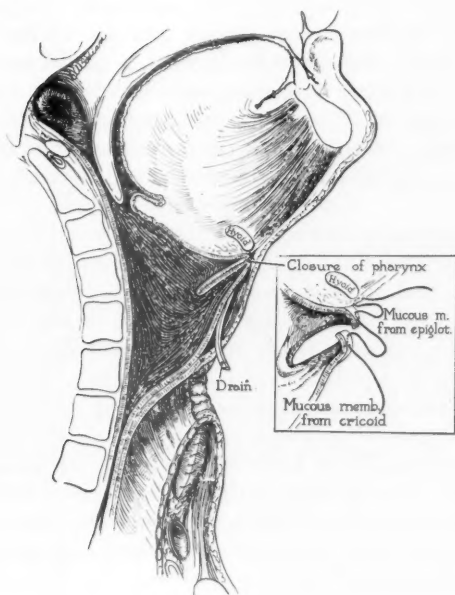


Fig. 3.—Closure of pharyngeal defect.

defects in the mucous membrane of the pharynx on each side are closed with inverting sutures. Each suture includes muscle which acts as support to the suture line. The wound is irrigated with tyrothricin. The strap muscles are plicated and the skin closed with interrupted sutures. A small protective wick is placed in the lower part of the wound. The skin around the tracheotomy opening is inverted into the trachea with interrupted sutures. A feeding tube is usually not used.

In any operation of this magnitude, success depends on following basic surgical principles. Traumatization of tissues with clamps or retractors, the use of high frequency cautery for hemostasis, or the leaving of pockets or dead space predispose to poor healing and wound infection.

Postoperatively these patients require little care. They are permitted to drink fluids the day of operation and are usually up in a wheel chair the second or third postoperative day. Supplementary fluids are given intravenously for the first two days, after which sufficient amounts of high caloric liquid diet can be taken by mouth.

There is very little coughing and little suctioning is required if care is taken to prevent blood from getting into the trachea at the time of operation. Since there is little coughing, a special nurse is usually not essential. The small protective drain is removed the day after operation. Penicillin is usually given prophylactically. However, in cases in which it was omitted, there were no more complications than in those in which it was given.

The postoperative course of the last 27 consecutive total laryngectomies performed at The Johns Hopkins Hospital are summarized in Charts 1, 2, and 3. These were all cases of squamous carcinoma. A number of these patients were elderly and feeble; a number also had serious ailments such as diabetes, arteriosclerosis, and heart disease. The operative mortality was zero. There were no cases of shock, postoperative hemorrhage, or pneumonia. In none was there more than a degree or so rise in temperature at any time. Of the cases summarized in Chart 1, there were four with some breakdown of the wound. One of these patients had received considerable irradiation therapy previous to the operation, and one was a severe diabetic. In all of these four cases, the wound had healed before the patient left the hospital.

In the cases shown in the last two charts, the wounds were irrigated with tyrothricin (diluted with distilled water 1:1000) during the operation at the time of the closure of the pharynx. Those shown in the third chart received systemic penicillin as well. In these groups of cases in which tyrothricin was used locally in the wound, there was complete absence of wound infection or other complications. The patients' stays in the hospital were relatively short, ranging from 8 to 13 days. The fact that these patients recover so promptly following their operation and their relative lack of discomfort minimizes the psychological trauma and makes it possible to institute early measures of rehabilitation.

There has been no effort in this paper to present percentage of cure since many of the patients have not been followed for more than a year or so. However, there have been no more early recurrences with the method described than the number reported by other workers using other techniques.

#### DISCUSSION

The main criticism which has been directed at the operation described in 1938 by Crowe and Broyles is that there is certain to be

contamination of the wound by secretions from the mouth during the removal of the larynx. In order to circumvent this hazard, in many clinics a clamp is used to close off the pharynx before the larynx is removed. In this technique, the larynx is dissected from below upwards, the hyoid is sectioned, and after the larynx is freed from the inferior constrictors, a clamp is applied across the mucous membrane. After this, the larynx is removed. The mucous membrane is sutured before the clamp is released.

There are certain very obvious disadvantages to this procedure. First, there is danger of aspiration of blood into the trachea during the whole period of dissection of the larynx. Second, the hyoid must be sectioned. Third, it is impossible to preserve as much of the normal mucosa of the pharynx as with the Crowe-Broyles technique. Fourth, the pharyngeal defect is pulled together under tension and is closed longitudinally instead of horizontally. Fifth, there is danger of leaving devitalized tissue in the suture line as a result of trauma from the clamp.

In reviewing the results obtained by the Crowe-Broyles technique when chemotherapy is employed, one must conclude that the danger of wound infection from the opening into the pharynx is unimportant. We feel that the crushing of mucous membrane by the clamp and closure of the mucous membrane of the pharynx under tension are much more conducive to breakdown of the wound than is contamination of the wound from the mouth. We believe that the advantages of preservation of the anatomic structures of the neck which are gained by the modified Crowe-Broyles technique make this the operation of choice in selected cases for total laryngectomy.

#### SUMMARY

1. A modification of the Crowe-Broyles technique for total laryngectomy is described which permits complete mucous membrane closure of the pharyngeal defect after removal of the larynx.

2. The postoperative courses of the last 27 consecutive total laryngectomies at The Johns Hopkins Hospital are reviewed. The effectiveness on wound infection of the prophylactic use of tyrothricin during the operation is demonstrated.

It is concluded that the operation as described reduces to a minimum postoperative complications and greatly shortens the recovery period.

JOHNS HOPKINS HOSPITAL.

CHART 1

PATIENT	DIAGNOSIS	CHEMO- THER.	POSTOPERATIVE COURSE						POST OPERATIVE DAY		
			SHOCK	COUGH	FEVER	WOUND INFE- CTION	FISTULA	NASAL FEED- ING	LIQUID DIET	OUT OF BED	DISCHARGED
H.K. AGE 63	SQUAMOUS CARC.	SULFA DIAZ.	0	SLIGHT	SLIGHT	0	NO	YES	2ND.	8TH.	16 TH.
O.P. AGE 49	SQUAMOUS CARC. LYMPHOS.	"	0	"	"	0	NO	NO	5 TH.	---	33 RD.
E.P. AGE 47	SQUAMOUS CARC.	SULFA IN WOUND	0	"	"	0	NO	NO	2 ND.	4 TH.	13 TH.
G.F. AGE 56	"	SULFA DIAZ.	0	"	"	YES	YES	NO	2 ND.	8 TH.	24 TH.
A.H. AGE 62	"	SULFA THIAZ.	0	"	"	YES	YES	YES	9 TH.	5 TH.	25 TH.
J.G. AGE 61	EPIDERM. CARC.	"	0	MOD.	MOD.	0	NO	YES	2 ND.	4 TH.	16 TH.
J.V. AGE 56	"	NONE	SLIGHT	"	"	YES	YES	YES	2 ND.	4 TH.	37 TH.
C.W. AGE 69	SQUAMOUS CARC.	SULFA DIAZ.	0	SLIGHT	SLIGHT	YES	YES	YES	3 RD.	3 RD.	44 TH.
T.S. AGE 77	"	NONE	0	"	"	0	NO	NO	4 TH.	4 TH.	21 ST.
J.M. AGE 52	EPIDERM. CARC.	NONE	0	"	"	0	NO	NO	3 RD.	4 TH.	22 ND.



CHART 2

PATIENT	DIAGNOSIS	CHEMO- THER.	POST OPERATIVE COURSE						POST OPERATIVE DAY		
			SHOCK	COUGH	FEVER	WOUND INFE- CTION	FISTULA	NASAL FEED- ING	LIQUID DIET	OUT OF BED	DISCHARGED
L.R. AGE 61	SQUAMOUS CANC.	TYRO. SULFA	0	SLIGHT	SLIGHT	0	NO	NO	3 RD.	4 TH.	10 TH.
H.B. AGE 24	"	"	0	"	"	0	"	"	2 ND.	4 TH.	13 TH.
J.F. AGE 57	"	"	0	"	"	0	"	"	3 RD.	4 TH.	9 TH.
A.B. AGE 57	"	"	0	"	"	0	"	"	2 ND.	3 RD.	9 TH.
W.F. AGE 49	"	"	0	"	"	0	"	"	2 ND.	4 TH.	8 TH.
F.T. AGE 30	"	"	0	"	"	0	"	"	2 ND.	5 TH.	11 TH.
J.J. AGE 59	"	"	0	"	"	0	"	"	1 ST.	5 TH.	10 TH.
L.D. AGE 52	"	"	0	"	"	0	"	"	3 RD.	6 TH.	9 TH.
A.W. AGE 54	"	"	0	"	"	0	"	"	3 RD.	4 TH.	9 TH.
A.E. AGE 58	"	"	0	"	"	0	"	"	2 ND.	3 RD.	9 TH.

CHART 3

PATIENT	DIAGNOSIS	CHEMO- THER.	POST OPERATIVE COURSE						POST OPERATIVE DAY		
			SHOCK	COUGH	FEVER	WOUND INFE- CTION	FISTULA	NASAL FEED- ING	LIQUID DIET	OUT OF BED	DISCHARGED
L.M. AGE 68	SQUAMOUS CARC.	TYRO. PEN.	0	SLIGHT	SLIGHT	0	NO	NO	2 ND.	4 TH.	9 TH.
J.F. AGE 45	"	"	0	"	"	0	"	"	2 ND.	3 RD.	12 TH.
J.M. AGE 80	"	"	0	"	"	0	"	"	3 RD.	9 TH.	16 TH.
I.B. AGE 63	"	"	0	"	"	0	"	"	2 ND.	5 TH.	7 TH.
F.E. AGE 54	"	"	0	"	"	0	"	"	2 ND.	3 RD.	12 TH.
A.P. AGE 64	"	"	0	"	"	0	"	"	3 RD.	3 RD.	15 TH.
M.S. AGE 53	"	"	0	"	"	0	"	"	2 ND.	3 RD.	10 TH.

## LIX

### THE OPEN APPROACH TO ARYTENOIDECTOMY FOR BILATERAL ABDUCTOR PARALYSIS, WITH A REPORT OF TWENTY-THREE CASES

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Great interest was initiated in plastic repair of the larynx in cases of bilateral abductor paralysis by King's<sup>1, 2</sup> original work.

Morrison's<sup>3</sup> description and careful analysis of 23 cases of the procedure described by King has shown that the use of the omohyoid muscle is not essential to the rotation and lateralization of the disarticulated arytenoid cartilage.

Kelly's procedure<sup>4, 5</sup> of arytenoidectomy via a window made through the thyroid cartilage has also resulted in a large series of successful cases in his hands.

Orton,<sup>6</sup> in describing his modification of the extralaryngeal approach to arytenoidectomy, stated that the first step in the attack on the arytenoid itself must be proper exposure. This he accomplished by removal of the lateral half of thyroid ala cartilage. The thyro-arytaenoideus muscle is then sutured to the external perichondrium and the anterior split sternothyroid and thyrohyoid muscles.

In January 1946 the author<sup>7</sup> published a preliminary report on a modification of the extralaryngeal approach to arytenoidectomy, in which a more open approach and a wider field were advocated for the complete removal of the articular part of the arytenoid cartilage and the fixation of the vocal cord laterally to the thyroid cartilage.

This paper is a further elaboration of that technique as carried out by the author and several other laryngeal surgeons at the Columbia Presbyterian Medical Center, together with a report of cases graciously contributed by Dr. Fletcher D. Woodward of the University of Virginia and Dr. Francis E. LeJeune of the Oschner Clinic in New Orleans.

The end results of 14 cases which have been under our own observation have been studied. A group of nine cases collected in answer to a questionnaire sent to other surgeons is also reported.

*Procedure.*—If a preliminary tracheotomy has not been done, the patient is prepared under local anesthesia with the placement of an intratracheal tube (under guidance of the laryngoscope). The tracheotomy may then be done under local anesthesia, or intravenous anesthesia may be started and the tracheotomy done under general anesthesia.

Following the tracheotomy an incision is made along the anterior border of the sternocleidomastoid muscle at the level of the upper edge of the thyroid cartilage and carried down to the level of the cricoid cartilage (Fig. 1). (The transverse incision located one third the way down from the upper edge of the thyroid cartilage is optional.)

The sternocleidomastoid muscle is retracted, exposing the posterior edge of the lateral thyroid cartilage (Fig. 2), with the thyrohyoid muscle attached anterior to its posterior edge and the inferior pharyngeal constrictor muscle attached to its posterior edge and to the inferior cornu. The attachment of the inferior cornu to the cricoid cartilage is a key landmark.

A vertical incision is made along the posterior edge of the lateral thyroid cartilage and the inferior cornu down to and through the perichondrium. The inferior constrictor is separated posteriorly; the cartilage is hugged closely and the perichondrium elevated around the posterior edge onto its mesial side sufficiently to free it of inferior constrictor attachments.

The facet-like joint between the inferior cornu and the cricoid cartilage is then separated (Fig. 3). The incision is carried through the perichondrium on the lateral wall of the cricoid cartilage and continued vertically upward until the subperichondrial dissection of the arytenoid cartilage has been accomplished. When the latter has been done, the joint is disarticulated. A traction ligature is then placed around the midpart of the arytenoid and the cartilage is rotated laterally (Fig. 4). With the aid of this traction ligature the vocal process can be well exposed. A curved atraumatic needle with single 0 chromic gut is passed around the vocal process, care being taken to keep it in the submucosa and to pass it through and include some of the fibers of the vocalis and the thyro-arytaenoideus muscles. After the placement of this suture all of the arytenoid cartilage is removed except the nonarticular part associated with the vocal process. The cord is then drawn laterally and tied around the inferior

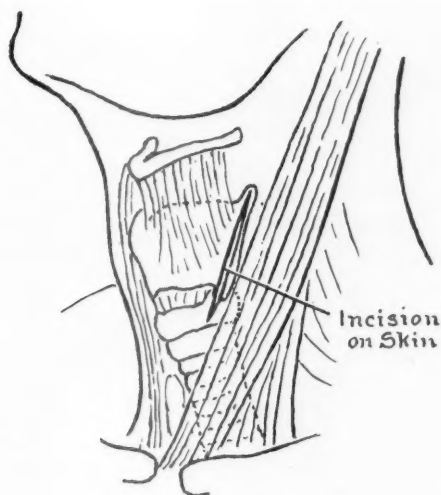


Fig. 1.—Site for the cutaneous incision.

cornu of the thyroid cartilage (Fig. 5), and this in turn is reinforced by anchoring the suture to the anterior edge of the sternocleidomastoid muscle.

Before the wound is closed, the larynx is inspected with the laryngoscope and a careful note made of the position of the cord.

Closure is made by bringing the inferior constrictor muscle back into place with a few separate sutures. Interrupted sutures close the skin, a Penrose drain being left in the lower end of the wound, which is removed on the fourth postoperative day.

#### ANALYSIS OF CASES

*Group I\**—Group I was comprised of 14 patients who were either operated upon by the author or came under his personal observation through follow-up examinations. A study of this group resulted in the following findings:

These 14 patients averaged 44 years of age. There were nine women and five men. Twelve of the patients gave the usual etiolog-

\*Cases were contributed to this series by the author and the following surgeons: Dr. John D. Kernan, Dr. Alexander D. Ghiselin Jr., Dr. Herbert Friedman. Also one case by the late Dr. James O. MacDonald.

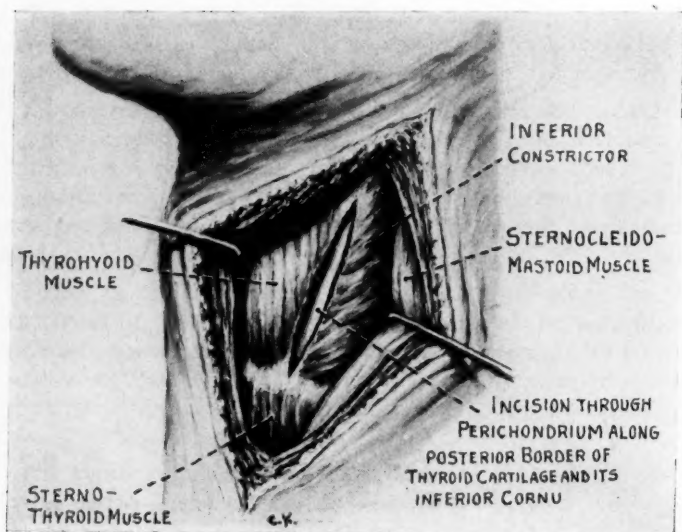


Fig. 2.—An incision has been made along the posterior border of the lateral thyroid cartilage and the inferior cornu down to and through the perichondrium.

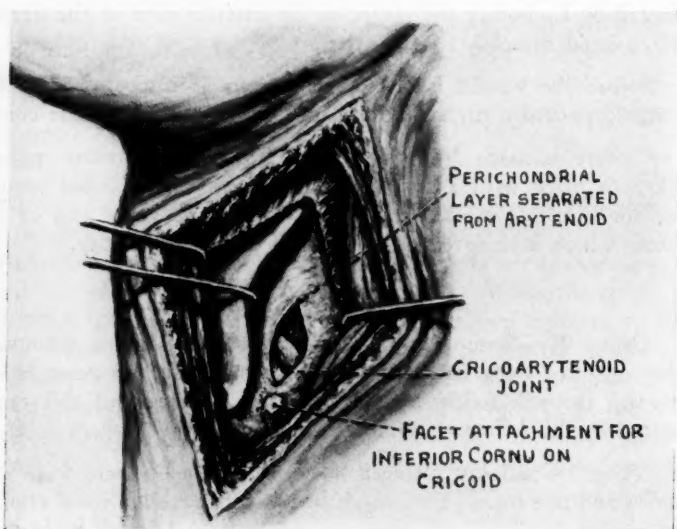


Fig. 3.—The facet-like joint between the inferior cornu and the cricoid cartilage is then separated.

ical history of dyspnea and voice changes following a thyroidectomy. Only two had central nervous system changes responsible for their paralysis.

Nine of the patients had their tracheotomy done within a few days or weeks before the arytenoidectomy. Five had their tubes introduced at the time of the arytenoidectomy. Three had had tracheotomies in years past and the tube had been removed. While some of these patients had managed to get along, they all had been restricted as to the extent of their activities and they were in particular distress during upper respiratory infections. None had been able to fulfill all regular activities.

In all but two of the cases drains had been placed in the lower end of the wound. One of these two patients developed a hematoma of the laryngeal tissues which necessitated operating on the other side, at which time a successful result was obtained. The surgeon who did this operation had had one good result on a previous case without the use of a drain. The drain and sutures were removed on the fourth and fifth days, respectively.

There was one death. This occurred on the third postoperative day when efforts were being made to replace a tracheotomy tube which had become dislodged. Hemorrhage developed during the procedure and the patient died from asphyxiation and hemorrhage in spite of heroic efforts and aspiration via the bronchoscope which was close at hand. The tracheotomy in this case had been difficult at the time of operation as there was considerable distortion of the trachea which took a very deep course. This patient had had a tracheotomy 30 years previously.

In 11 cases the tracheal cannulas were removed in an average of 28 days. The earliest one was removed on the tenth postoperative day and the one in for the longest time was taken out on the forty-ninth day. All tubes were corked for three to four days before removal; then if no dyspnea followed moderate exercise and if mirror examination of the larynx showed no evidence of laryngeal edema, the tubes were removed.

Two patients still wear their tubes. In both of these cases there is better than a 4 mm. space in the posterior glottic chink. No obstruction was found after inspection by both direct laryngoscopy and bronchoscopy. Both tubes were corked for several days at a time but the patients refused to go without their tubes permanently. They have been checked by psychiatrists and their condition diagnosed as psychoneurosis, anxiety state. At the present time one of



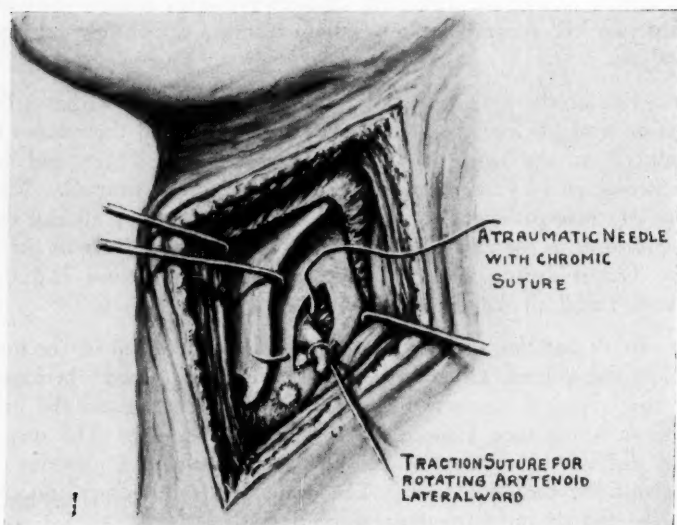


Fig. 4.—A traction ligature is placed around the midpart of the arytenoid and the cartilage rotated laterally.

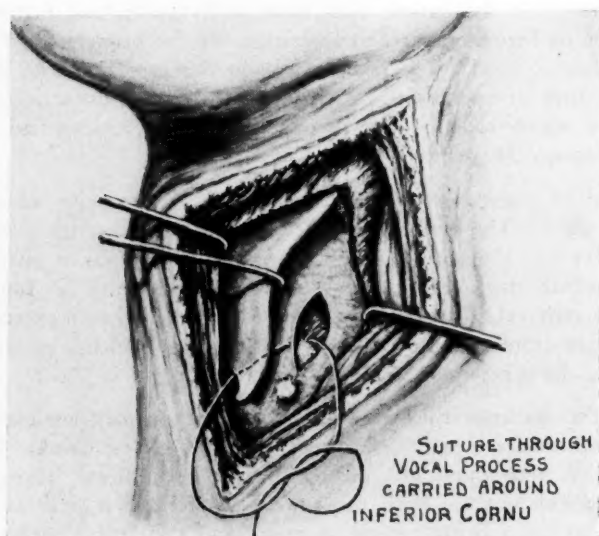


Fig. 5.—The cord is drawn laterally and tied around the inferior cornu of the thyroid cartilage.

these patients is making a better adjustment at home and is again corking her tube for increasing intervals preparatory to trying to get along without it. This complication is a real one and will probably always offer a problem, at least in a small percentage of cases.

The average estimated size of the posterior glottic chink or point of maximum width was 4.5 mm.

Seven patients had improved voices. Five had only adequate voices. Two of these with adequate voices are still wearing canulas. One who was classified as having an adequate voice had had both sides operated upon because of a hematoma following the first operation. The fourth and fifth patients with only adequate voices, had this result because of a glottic chink of 6 mm. width.

One patient, who is very happy with the end result, carries on his business as a salesman and does well in all his activities, but his voice is definitely worse and very husky. His glottic chink measures 8 mm.

Eleven of the 13 living patients are satisfied with the results of their operation. We are still hoping that psychiatric care may improve the two patients who still wear their tubes.

Complications which have not already been mentioned include one stitch abscess and one case of bronchopneumonia. One patient who had only a 3 mm. chink has been troubled with asthmatic attacks, but has improved since being under the care of an allergist.

In the average case a temperature of 101° F. developed on the second postoperative day; it gradually subsided to normal about the fourth postoperative day.

All patients received chemotherapy. Thirteen of these operations were done at the Presbyterian Hospital and in none of these cases was it necessary to use a feeding tube. One patient who was operated on at another hospital developed a complicating bronchopneumonia and was fed by an intranasal feeding tube.

*Group II\**—Group II was comprised of nine cases the reports of which were collected in answer to a questionnaire sent to other surgeons who have followed the technique described.

It is interesting to note that, with very few exceptions, the general pattern in Group II is nearly the same as our own experience with Group I.

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\*We are very much indebted also to Dr. Fletcher D. Woodward, Dr. Francis E. LeJeune and Dr. Alexander D. Ghiselin Jr. for these cases and reports.

All Group II cases were in females whose average age was 44. Seven operations were performed on the right side and two on the left. Eight cases were the result of postoperative complications following thyroidectomies. One case was that of a central nervous system lesion of unknown origin.

Seven patients had tracheotomy tubes placed one week to 18 months prior to the arytenoidectomy and in two cases the cannulas had been placed at the time of arytenoidectomy.

In this group the drains were removed on the fourth day and the sutures on the fifth day, on the average.

The average time for removing the cannula was the twenty-fifth postoperative day.

In this series the voice results were classified as: four better, four adequate, and one worse. In the last mentioned case the patient was satisfied with the result in spite of the husky voice and again this occurred as the result of a wide glottic chink. In five of the cases the posterior aspect of the glottic chink was estimated to be 3.2 mm. in width on the average. In the four cases reported by Dr. LeJeune an estimated width of the glottic chink was not given; they were classified as having adequate airway for all activities.

All nine patients in this group were satisfied with the results. Three of the nine were fed with feeding tubes. All had chemotherapy

One patient whose first operation had been a failure was operated on on the other side later with an excellent result. One patient had a stitch abscess and one a severe upper respiratory infection.

Combining the two groups representing 23 cases, only two patients, or about nine per cent, are wearing tubes and this is not the fault of any failure of the surgical procedure, but is the result of the mental condition of both patients.

*Comments.*—The incision along the anterior border of the sternocleidomastoid muscle seems closer to the area which we wish to expose, although some surgeons use a transverse incision one third the way down the thyroid cartilage.

The use of the atraumatic needle was not described in the original procedure; however, this has proved a great help and makes tearing of the laryngeal mucosa much less likely.

The suture which is tied around the inferior cornu lateralizing the vocal cord probably does not need to be re-enforced by anchoring to the anterior edge of the sternocleidomastoid muscle; however, if the cornu has been weakened or fractured, this is a good precaution to take. In one of our cases the cornu was completely broken off and in this the suture was brought through a small  $\frac{1}{8}$  inch drill hole  $\frac{1}{4}$  inch anterior to the posterior edge of thyroid cartilage.

In one case in which the thyroid cartilage was oval in shape and showed considerable posterior constriction, exposure was considerably improved by cutting through the superior cornu and releasing tension.

There is nothing to be gained by too early removal of the cannula. Certainly it is better not to remove it until at least four days of full corking and after the patient has been up and around carrying on a moderate amount of physical activity. The patient is cautioned to rest and not to attempt to use the voice the first ten days.

The resulting voice apparently depends entirely on getting adequate airway and at the same time not too wide a glottic chink. A space of 3 to 4 mm. is adequate. Such a space always results in a good speaking voice. If the space is wider than 6 mm., then the voice definitely suffers in quality. The airway after all is the paramount problem. The voice, while important, is secondary.

In cases in which both sides have been operated upon or those in which the glottic chink is 7 or 8 mm. wide, the patient can train the false cords to function and thus obtain an adequate speaking voice.

Postoperative edema has not been a complication to contend with in the majority of these cases. Of twenty-three cases in only four was an intranasal feeding tube needed. The need of psychiatric care should be stressed for those few patients who refuse to do without their tubes in spite of adequate airway.

#### SUMMARY

The open approach to arytenoidectomy has now been done by several surgeons throughout the United States during the past three years. The results of these cases in varied hands indicate the appeal of a wide exposure of the operative field and the general success of the technique described.

156 EAST 37TH STREET.

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SURGERY OF THE NASAL SEPTUM—NEW OPERATIVE  
PROCEDURES AND INDICATIONS

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The submucous resection of the cartilage of the nasal septum was performed and described by Ingals<sup>1</sup> of Chicago in the year 1882. Boeninghaus<sup>2</sup> and Krieg<sup>3</sup> and others extended the procedure to include the perpendicular plate of the ethmoid and the vomer and the total procedure found its completion in the work and writings of Freer<sup>4</sup> in 1902.

Killian<sup>5</sup> in 1904 and many others in all parts of America and Europe added refinements and modifications but not until rather recently has anything essentially new been added to extend the usefulness of the operation. As is well known, operations on the septum in the hands of most otolaryngologists usually do not include removal of the bone and cartilage just beneath the dorsum, and most frequently operative procedures on the caudal end of the septum, though indicated, are meticulously avoided.

These two restrictions prevail because saddle noses and retracted columellas otherwise frequently occur. It was Freer who first pointed out that these deformities are not the result so much of the removal of structural supports but instead are the result of post-operative scar formation and subsequent cicatricial contraction; Fomon<sup>8</sup> more recently rediscovered and taught this dictum and suggested the prophylactic, namely, the replacement of bone and cartilage between the mucosal flaps and into the membranous septum and the columella. Though many before Fomon replaced bone and cartilage following the submucous resection, it was he who first insisted that restitution would prevent and could be used to correct postoperative deformities.

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The typical Freer or Killian operation starts with an incision near the mucocutaneous junction or more posteriorly. This does not easily permit procedures anterior to the incision where obstruction to breathing may be located. Also, this incision bisects one of the mucosal flaps, which has a twofold disadvantage. First, if the incision is well in the mucosa, the resultant scar constitutes an impediment to normal ciliary activity and, second—and this is very important for our purpose—a large flap to cover replaced bone, cartilage, or an acrylic or other implant has been purposely but needlessly sectioned.

Again Freer knew and wrote, and many have subsequently definitely corroborated him, that replaced cartilage will be well tolerated and supported in the intramucosal space if it is sufficiently covered with mucosa.

As we now perform the submucous resection of the nasal septum, the incision is made at the caudal end of the septum preserving all of the membranous septum.

This allows access to any or all parts of the nasal septum. The details were previously described<sup>6</sup> and are here briefly repeated.

1. Incision: The columella is pulled gently away from and to the left of the caudal end of the septum. This defines the edge of the septum on the right side. One-eighth of an inch behind this edge the incision is made through the skin and down to the cartilage on this side. The cut is made in two movements. Each approaches the middle, one starting from the tip area and the other from the region of the nasal spine of the maxilla. The skin of the right ala may be protected with a lid retractor.

2. Elevation of the Left Mucosal Flap: The columella is retracted to the left. The caudal end of the septum covered by fibrous tissue now lies exposed. The tissues are kept stretched, the fibrous layer over the septum edge is cut and the left side of the septum begins to be seen. With a straight stiff, sharp, round-ended knife (or the straight Freer septum knife) held almost perpendicular to the septum the first one-eighth inch of the cartilage is exposed. It is a great help to hold the cartilage steady by means of a hook passed through the thickness of the cartilage and the mucosa on the right side. Too much pull will cause the hook to tear through the tissues. Not until the blue color of the cartilage is well seen should one continue the elevation posteriorly. The mucosa just ventral to the center of the incision is frequently the easiest to elevate first. Having exposed the first one-eighth inch of the cartilage one can with



assurance continue to separate the first one-half inch. The skin and mucosa of this area are very adherent, especially near the nasal spine, and careful, sharp dissection and separation is imperative. After this the usual elevation (with sharp or dull, forward or backward elevators) is completed.

3. Elevation of Right Mucosal Flap: This is done in two ways depending on whether or not the caudal portion of the septum is to be incorporated in the operation.

If the caudal end of the septum is not included in the operation, the blades of the nasal speculum are inserted between the cartilage and the left flap and an incision in the cartilage is made caudal to the deformity which is to be corrected. Through this cartilage incision the right flap is elevated, as in the typical Freer operation, which then may be watched through the right nostril or by direct vision between the mucosal flaps.

If the caudal end of the septum is to be included in the operation, the elevation of the right mucosal flap is started just like the left one. The separation is then continued as on the other side and may be observed directly by placing a long-bladed nasal speculum between the cartilage and the right flap or via the right nostril as is done in the old operation.

4. Removal of Cartilaginous and Osseous Deformities: By placing a blade of a long nasal speculum on each side of the hard septum, the mucosal flaps are held away sufficiently to permit the removal of any part or all of the cartilage and bone. Ordinarily there should be no hesitancy in completely removing all bone or cartilage which interferes with the normal passage of air through the nose. If there is a weakness of the nasal dorsum, such as from a hump removal, congenitally small, short or thin upper lateral cartilages or impaired upper lateral cartilages which may follow injuries and inflammations, a sagging of the cartilaginous dorsum may be anticipated and adequate reinforcing procedures, such as dorsal and septal grafts, later instituted. Biting forceps should be utilized for careful removal of the ventral portion of the septum.

5. Replacing Bone and Cartilage with the Caudal End of the Septum Intact: Vaseline gauze strips are packed securely but not too tightly in each nasal cavity. The pieces of bone and cartilage which were removed are trimmed and thinned. The long nasal speculum is placed between the mucosal flaps, spread a little and the prepared pieces inserted. Only small, straight, thin pieces are used. If more material is needed, preserved septal or rib cartilage

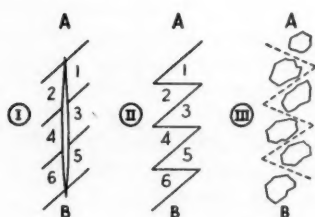


Fig. 1.—Contraction of skin from A to B (I) is corrected by a series of Z-plastic flaps (II). Similarly a straight contraction from A to B (III) is avoided by placement of small pieces of cartilage and bone which in effect act like a series of Z-plastic flaps.

may be added. The packing on each side will hold the grafts well in place. The edges of the incision are sutured.

The replaced autogenous bone and cartilage pieces between the mucosal flaps continue to live and grow. They prevent the flaps from becoming flaccid and by diminishing the quantity of post-operative scar formation help in preserving an adequate blood supply to the mucosa.

6. Replacing Bone and Cartilage When the Caudal Part of the Septum Has Been Removed: It is imperative to replace the cartilage of the anterior portion of the septum, not so much to provide a center support but to limit the amount of scar tissue which will form during healing and to prevent it from pulling in one continuous straight line which results in the maximum amount of distortion. The contraction of the scar tissue is the force that pulls down the lower part of the nasal vault and retracts the columella into the nose (Figs. 1 and 2).

To replace a large single piece of cartilage anteriorly Fomon teaches the following Galloway operation:

A large piece of septal cartilage (2 x 4 cm. or larger) is fashioned from the removed tissue or if this is not available, preserved septal or rib cartilage is used. The edge of the selected cartilage, which will become the caudal end of the septum, is carefully trimmed to fit into a pocket prepared in the membranous septum and the columella. Two double-armed sutures are passed through opposite corners of the cartilage which is then placed between the

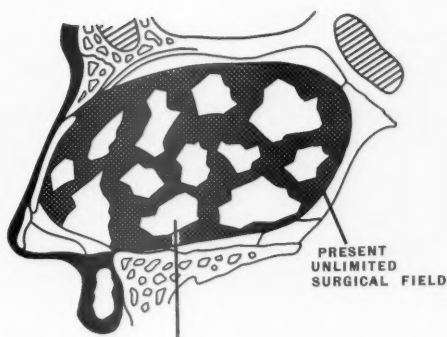


Fig. 2.—Postoperative contraction deformities prevented by replacing cartilage and bone pieces.

mucosal flaps. The needles are passed into the columella pocket and are brought out through the skin between the two medial crura, one ventrally and the other dorsally. By pulling on these sutures the cartilage is guided anteriorly into the columellar pocket and with two or three sutures through the septum joining the anterior and posterior edges of the original incision, the graft is held in place. The guide sutures are cut and removed. (Before fixing the graft in place we packed the nose on each side as in procedure No. 5 and the other pieces of cartilage and bone were replaced posteriorly as indicated.)

Several factors mitigate against the constant utilization of this procedure. The large cartilage frequently becomes twisted due to torsion or tilts and obstructs a nasal chamber, or both chambers. Because of its inclusion in the columella the cartilage moves and stretches the mucosa every time the tip of the nose is wiped or otherwise moved, as in the mechanics of making facial expressions.

The objective of reconstruction should be the retention or restoration of a normal columella, freely movable and adjacent to a membranous septum, which in turn is contiguous with a cartilage-bone nasal septum. Hence we prefer the following technique for reconstruction of the cartilaginous septum.

With the original incision properly made, cartilage may be replaced in the anterior portion of the nose without making a pocket

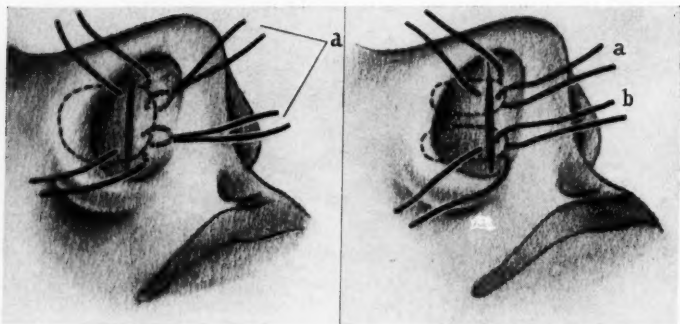


Fig. 3a.—Dotted circle indicates cartilage replacing caudal edge of septum. Guide sutures (a) are tied to each other. Other sutures hold cartilage in place and close original incision.

Fig. 3b.—Small pieces of cartilage replace caudal portion of septum. Guide sutures at (a) are tied; also those at (b). Other sutures as in Fig. 3a.

in the columella and generally without the necessity of introducing a batten (graft) into the columella. A large piece of cartilage is not used for the reasons mentioned above and also because a single small piece or several smaller pieces have proven to be sufficient.

Instead of making a pocket completely in the columella, the pocket is made only in the immediate proximal portion of the membranous septum. This is already accomplished if the incision and the elevation of flaps have been made as described.

A moderate-sized piece of cartilage or several small pieces are then fixed in this area by sutures (Fig. 3a and b)—or are just simply held in place with packing, as are the small pieces which are placed posteriorly. Whenever possible the original incision is closed with sutures.

Operations on the external nose must frequently be done at the same time as operations on the septum. If the bony vault of the nose is to be mobilized together with the removal of the major portion of the hard nasal septum, the relation of the septum to the upper lateral cartilages must be preserved or restored or at least the mucosal linings must be.

The upper lateral cartilages are wings off the main quadrilateral nasal septum cartilage. Cephalically they are attached to the under

or dorsal surfaces of the nasal bone. Laterally they are attached by fatty fibrous tissues to the pyriform crests. Within the nose the mucosa of the nasal septum is reflected over their dorsal surfaces and continues as the lining of the lateral surfaces of the nose and onto the floor of the nasal chambers.

Caudally the upper lateral cartilages are free, covered ventrally by surface skin and dorsally by the skin of the vestibules and the mucosa. The caudal edges can be seen by retracting the alae.

If a typical rhinoplasty is done (a hump removal, lateral osteotomies or separation of the upper lateral cartilages from the septum) together with a radical septum resection, no structure is left which will support the nose (outside of the lobule) and reconstruction is rendered most difficult.

The preservation of the upper lateral cartilage and nasal bone attachments to the septum helps support the nasal pyramid but, if these must be sacrificed, then their mucosal reflections should be preserved. This will allow the packing of gauze inside the nose which will help support the pyramid during the healing period.

The attachments or their mucosal reflections can be preserved in several ways:

- a. It may not be necessary to cut the attachments at all.
- b. Cutting only a part or parts of the attachments may suffice.
- c. The upper lateral cartilages may be cut by a ventral approach without cutting their mucosal reflections.
- d. By extending the original elevation of the septum mucosal flaps up to the juncture of the quadrilateral cartilage and the upper lateral cartilage and then cutting through the cartilaginous juncture, one can preserve the mucosal reflections.
- e. Attachments after being severed may be sutured to each other and to the septal flaps.
- f. If a hump removal is not indicated but a separation of the bones is, then this may be accomplished by chiseling the bones from between the mucosal flaps, which will preserve the mucosal reflections in the upper nose area.
- g. If the removal of a hump is indicated this may be done with a Kazanjian cutting forceps after the nasal bones have been separated (as described in f) and mobilized and the nose has been packed and the septum reconstructed.

The septum operation combined with rhinoplasty may be done after a complete transfixion incision through the membranous septum. Where a complete removal of the nasal septum is necessary we do not prefer this approach, first, because reconstruction is more difficult and, second, more of the blood supply has been disturbed.

Because the septum operation described permits surgery without many reservations and without fear of further deformities and increase in disturbances of growth and function, the indications for the operation have become extended and may be enumerated as follows:

1. Obstructions, deviations, spurs, and ridges, involving any part or all of the septum, which disturb the physiology of the nose may be removed and suitable replacements introduced.
2. Dislocations of the septum due to fracture which interfere with the adequate correction of recent or old traumatic deformities may be freely mobilized and repaired.
3. Septum surgery may be performed on children if nasal obstruction or deformity interferes seriously with respiration and ventilation and drainage of the nose and sinuses.
4. The septum operation may be performed together with partial or extensive rhinoplastic surgery.
5. This septum operation is of great value in connection with the correction of congenital nasal deformities, especially those occurring with hare-lips.
6. In surgical treatment of atrophic rhinitis (as described by Proud<sup>7</sup>), this operation offers the best chances for the preservation of mucosal flaps for adequate covering of acrylic implants.
7. Through the incision described, access to the dorsum of the nose is available for the introduction of dorsal grafts and implants used in correction of saddle deformities of moderate dimensions.

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## OSTEOMA OF THE FRONTAL AND ETHMOID SINUSES

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Osteomas of the ethmoid and frontal sinuses have been discussed in many papers, yet there are several questions which are not answered. Four cases which we have observed offer an opportunity to study particularly two questions: the treatment and the growth of osteomas. The presented cases do not permit conclusions concerning the origin of these tumors because in Case I there was a small osteoma of the frontal sinus which was not examined histologically. In the other cases the tumor was so large that no conclusions concerning its origin could be drawn.

CASE 1.—H. M., white male, aged 49, had measles, scarlet fever and mumps in childhood. From 1915 to 1921 his profession was boxing. After this period he frequently had slight head injuries. For eight or ten years he suffered from attacks of headaches, particularly when he was constipated. Occasionally he noticed neuralgiform pains which radiated from one side of the forehead to the other. For 15 or 20 years he has been suffering from sciatic neuralgia on the left side.

Examination on January 23, 1942, revealed that the forehead was slightly prominent and the veins of the skin of the forehead were dilated. The supraorbital arches were likewise prominent and thickened. There was a deviation of the nasal septum to the right, but there was no other pathologic condition in the nose. There was a chronic tubal suppuration in both ears and the Kahn test was negative. X-ray films taken in December 1941 showed a bony tumor which was adherent to the posterior wall of the frontal sinus close to the interfrontal septum. The tumor bulged into the right frontal sinus and pushed the anterior wall of the sinus outward and the interfrontal septum to the left. The tumor occupied the upper

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portion of the right frontal sinus and caused a thickening of the posterior wall in the inferior portion of the sinus. At the upper boundary of the frontal sinus there was no sharp margin between the cancellous bone of the tumor and that of the diploe of the frontal squama. The patient refused surgery. On March 28, 1942, a submucous resection of the nasal septum was performed. The headache was slightly relieved. The patient was seen again on February 5, 1947. He felt well. The bony tumor of the frontal sinus had not changed either in size or in shape.

*Comment.*—In this case the x-ray examination revealed a small osseous tumor in the right frontal sinus. It is likely that the tumor was covered by frontal sinus mucosa; that is, it was situated subepithelially. Kelemen<sup>1</sup> has examined a small osteoma of this type microscopically and found it to be covered by mucosa. These tumors are not uncommon. Saettler<sup>2</sup> reported 29 cases of this type. The tumor usually involved the posterior wall or the roof of the frontal sinus. In the presented case the tumor involved both the posterior wall and the roof. Most important is the finding on the x-ray films that the tumor did not change in size or shape in a period of five years. Saettler<sup>2</sup> likewise reports a tumor, the size of a pea, within the left frontal sinus of a man, aged 68, which did not change in a period of five years. Childrey<sup>3</sup> made the same observation. Saettler<sup>2</sup> reports another case of a man aged 19 years, in which there was a tumor the size of a pea which in a period of one and one-half years reached the size of a walnut. Although we do not feel entitled to question this finding, we wish to point out that the x-ray films showing the growth of the tumor were not made by exactly the same technique.

These findings prove that in the paranasal sinuses small osseous tumors occur which bulge into the sinus and are covered by the sinus mucosa. These tumors do not cause clinical symptoms and at least some of these tumors do not grow, certainly not in persons of 50 years or more. For this reason, a surgical removal of these tumors is not necessary. We believe that these small tumors are not actually neoplasms, but osseous hyperplasias which could be called exostoses, analogous to the exostoses of the temporal bones.

In other instances, particularly in young individuals, the exostoses of the frontal or ethmoid sinuses do become larger and form a typical osteoma. Case 2 shows an example of this type of osteoma.

CASE 2.—P. J., white male, aged 17 years, noticed a tumor at the inner angle of the left eye for the first time eight months pre-

viously. The tumor grew gradually, pushing the left eye lateralward and causing double vision. There was no pain. There was epiphora on the left side and a purulent discharge from the left nostril.

On admission on May 26, 1939, a deviation of the septum was discovered, obstructing the right nostril. On the left side the middle turbinate was edematous and there was some pus in the middle meatus. In the inner angle of the left eye a tumor, hard in consistency and immovable, was palpable. The left eye was slightly displaced lateralward and forward. X-ray film showed a bony tumor in the left ethmoid and a haziness of both maxillary sinuses. On June 1, 1939, a Killian incision was made at the inner angle of the left eye. The tumor was immediately exposed, indicating that it had destroyed the frontal process of the maxilla. The tumor was easily removed leaving a cavity with the following walls: mesially the mucous membrane of the lateral wall of the nose, laterally the periosteum of the orbit which was perforated by the tumor in the posterior part, superiorly the roof of the ethmoid and the mucous membrane at the floor of the left frontal sinus, inferiorly the roof of the maxillary sinus, and posteriorly the anterior wall of the sphenoid. In the frontal sinus, the floor of which was destroyed by the tumor, there was some mucus. The dura was not exposed. The mucosa of the lateral wall of the nose was incised and the cavity was drained into the nose. Uneventful recovery ensued.

*Comment.*—In this case, the osteoma had destroyed the frontal process of the maxilla, the floor of the frontal sinus, the lamina papyracea and a small part of the periosteum of the orbit. For this reason the tumor caused ocular symptoms which were progressive over a period of eight months. This was the indication to perform an operation.

The operation must be performed if with an osteoma of the frontal or ethmoid sinuses ocular symptoms are noticeable, because these symptoms indicate the invasion of the orbit by the tumor. However, we feel that one should not wait for the manifestation of these symptoms. The tumors should be surgically removed whenever there is evidence of expansion, whether there are ocular symptoms or not. If an osteoma is growing at all, it certainly will extend some day beyond the boundaries of the sinus. This would not imply great risk, if the tumor would extend invariably into the orbit. However, the osteoma may extend toward the cranial cavity and not toward the orbit (Cases 3 and 4). In this case, clinical symptoms become evident in a late period of the illness. When

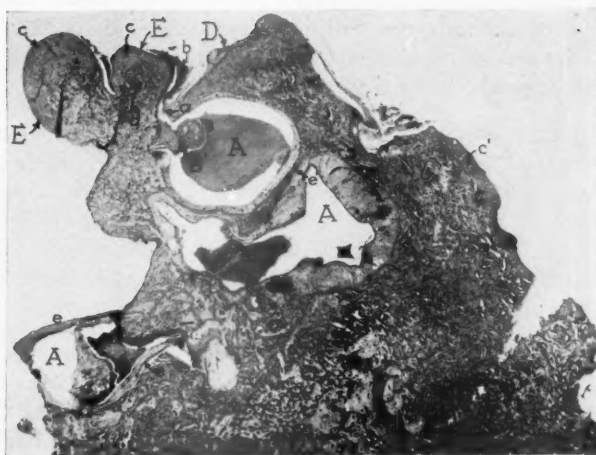


Fig. 1, Case 3.—*A*, ethmoidal cells with swollen mucosa and pus in the lumen; *E*, exostosis-like nodules; *E*<sub>1</sub>, exostosis-like nodule bulging into an ethmoidal cell; *D*, dura, inflamed, *a*, communication between cranial cavity and ethmoidal cell; *b*, pus; *c*, periosteal compacta; *c*<sub>1</sub>, secondary compacta, presented in Fig. 3 in higher magnification; *d*, spongy core; *e*, normal wall of ethmoidal cell; *e*<sub>1</sub>, normal wall of ethmoidal cell which shows in *x* a thickening and an incipient change into cancellous bone. The other walls of the cell are made up by the osteoma.

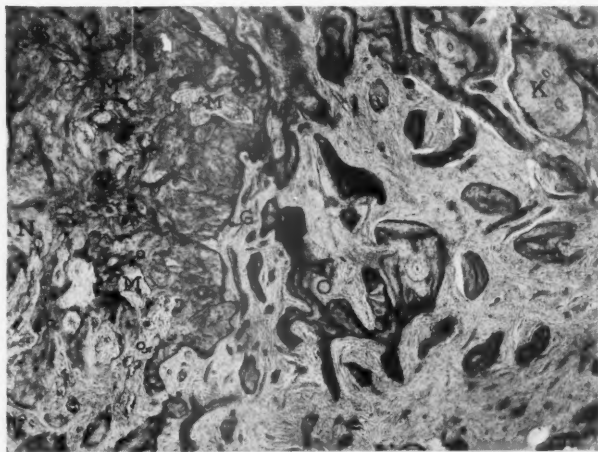


Fig. 2, Case 3.—*G*, Grenzschleide; *M*, marrow spaces containing fibrous tissue and blood vessels, which invade the necrotic compacta *B* and form new bone; *N*, newly formed woven bone; *o*, osteoid substance; *O*, osteoplastic ossification within the connective tissue; *K*, bone trabeculae consisting of lamellar bone.

this is so, an operation may have to be performed after the osteoma has invaded not only the cranial cavity but also the brain. Therefore, it is wiser to remove an osteoma whenever it shows a tendency to expand, regardless of ocular symptoms.

CASE 3.—Male, white, aged 34, was removed unconscious from his home on May 27, 1942. He was suspected of having attempted suicide with sodium fluoride poisoning. When he was admitted to the hospital, he was very dyspneic, his temperature was 97.6° F. and his pulse 110. He was in a coma. His head was turned to the left, the eyes turned upwards. The reflexes were exaggerated on the left side, the pupils were round and equal and did not react. The spinal fluid was bloody. Soon after his entrance into the hospital he died.

At autopsy a minimal amount of blood was found in the right temporal muscle when the scalp was reflected. There was no fracture of the calvarium or the base of the skull. At the base of the skull, in the area of the left cribriform plate, there was a bony outgrowth which extended into the undersurface of the left frontal lobe for a distance of 1.5 cm. The tumor occupied the area of the left ethmoid and sphenoid sinuses and extended backward to the clinoid process of the sella turcica. The tumor was removed and measured 4 x 3 x 5 cm. The dura mater and the superior longitudinal sinus were unchanged on gross examination. The cerebral hemispheres showed evidence of bulging in the frontal, temporal and parietal regions. There was a greenish liquid material in the subarachnoid space in both cerebral hemispheres and the lateral ventricles of the brain, indicating a diffuse purulent meningitis. On the undersurface of the left frontal lobe, in apposition to the bony tumor in the left cribriform plate, there was a depressed area with softening of the brain tissue.

There was a hyperemia of both lungs and hemorrhage in both lower lobes, a follicular hyperplasia of the spleen, a hyperemia of the mucosa of the stomach and a grade I sclerosis of the coronary arteries.

*Microscopic Examination:* The tumor consists chiefly of cancellous bone, the structure of which is not uniform. Close to the surface of the tumor the bony trabeculae are of considerable thickness, consist essentially of lamellar bone which stains with eosin and may contain haversian systems. Between the trabeculae there are a small amount of connective tissue, dilated capillaries and osteoblasts. This renders the spaces between the trabeculae very narrow, indicating a transformation of the cancellous bone into compact

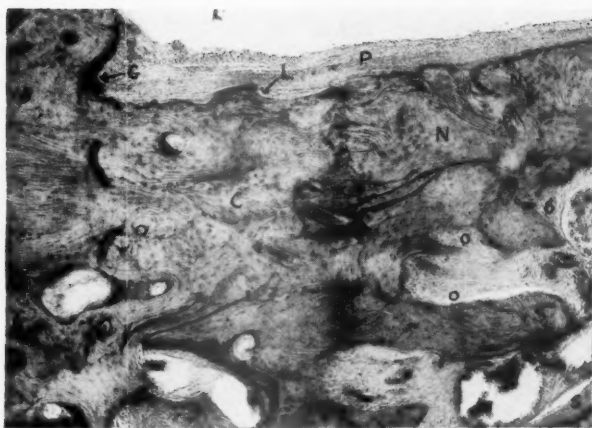


Fig. 3, Case 3.—P, periosteum; G, blue *Grenzschleide*; L, Howship's lacuna filled with osteoblasts; C, secondary compacta; S, cancellous bone in the process of being transformed into secondary compacta; n, network bone; o, osteoblasts.

bone. In fact, at several sites the surface of the tumor consists of a layer of compact bone which has been formed by a fusion of bone trabeculae (Fig. 1). This layer of compact bone contains short bone lamellae which frequently surround capillaries or small marrow spaces, occasionally forming haversian systems. We call this type of solid bone secondary compacta—"secondary" because it is formed by a transformation of cancellous bone (Fig. 3).

In contradistinction to the secondary compacta bone there is on other sites of the surface a periosteal compacta (Fig. 1 and 5): the periosteum lays down a layer of compact bone which contains Volkmann's blood vessels and long general-lamellae. The lamellae of the periosteal compacta do not surround blood vessels or marrow spaces, but cover the spongy core of the tumor. The periosteal compacta does not form by a fusion of bone trabeculae but consists of solid bone when it is laid down. The deposition of periosteal compacta causes the tumor to expand. In fact, at several sites so much periosteal compacta has been laid down that it forms exostosis-like nodules at the surface of the osteoma. However, there is apparently a kind of equilibrium between deposition and absorption of compact bone, because the compact bone, which has been laid down by the periosteum, is soon invaded by the connective tissue of the tumor,



which splits up the compact bone by the activity of osteoclasts (Fig. 1) and transforms it into cancellous bone. It is interesting to note that there is an opposite course of development as far as the periosteal and the secondary compacta are concerned. The former is laid down as solid bone and is transformed into cancellous bone; the latter is laid down as cancellous bone which forms a compact bone by the fusion of the trabeculae.

The core of the tumor shows a great amount of connective tissue with a normal number of nuclei, many dilated blood vessels and recent hemorrhages. Within the connective tissue there is calcium and newly formed bone. The latter forms trabeculae which are basophilic, consist exclusively of woven bone, show aplastic boundaries and are frequently poor in osteocytes. If there are only a few trabeculae, the tissue is similar to an ossifying fibroma. If a great amount of bone is formed, the trabeculae may fuse, forming a small area of compact, woven and necrotic (acellular) bone (Fig. 2). Parts of this compact bone become resorbed by the surrounding connective tissue and the remnants of the acellular bone serve as a matrix for the deposition of newly formed bone. There is no distinct boundary between the area with thick trabeculae and the area with slender trabeculae; nevertheless, the distinction is easily made by the oxyphilia of the former and the basophilia of the latter area. At sites where no compact bone is found, the spongy core of the tumor extends up to the surface (Fig. 1).

The ethmoid cells at the surface of the osteoma contain pus (Fig. 1). The mucosa is edematous, slightly inflamed and the epithelium is columnar. The osseous walls of the ethmoid cells consist either of cancellous bone of the osteoma which may bulge into the lumen of the cell or of bony plates which, under normal circumstances, form the septa between the ethmoid cells. However, certain findings indicate that these bony plates are not entirely normal. Occasionally there is a localized thickening of the plate (Fig. 1). Connective tissue originating in the mucosa invades the thickened areas, ushering in the transformation of compact into cancellous bone; or the slender bony plates fuse with the spongiosa of the tumor and are gradually transformed into cancellous bone.

*Comment.*—Although there is no exact history available, one can reasonably assume that in this case the osteoma did not cause marked clinical symptoms, not even ocular symptoms. Nevertheless, the autopsy revealed an osteoma of the ethmoid which had broken through the dura of the anterior fossa, had caused a malacia at the base of the frontal lobe and had ultimately caused a menin-



gitis. The sudden death was believed to be caused by sodium fluoride, until the autopsy revealed the actual cause.

Meningitis caused by osteoma of the sinuses is not frequent. Teed<sup>4</sup> found among 321 cases of osteoma, nine cases of brain abscess and one case of meningitis, the latter occurring after the operation for the osteoma. Of the four cases of Cushing<sup>5</sup> two patients died from meningitis, one following an operation. Birch-Hirschfeld<sup>6</sup> believes that mortality from osteomas which were not operated on is about 48 per cent. Most dangerous are the osteomas of the posterior ethmoid or the sphenoid because they may cause an intracranial complication even if they are small.

An intracranial infection may occur if the osteoma does not occupy the entire sinus and the rest of the sinus becomes acutely inflamed. This type of infection is dangerous because the osteoma narrows the space in the sinus and interferes with drainage, thus encouraging retention of pus and the progress of the infection toward the cranium. In other instances the osteoma has broken through the dura, exposing the subdural spaces and the brain to the infection in the nasal cavities. In these instances a slight increase in the virulence of the bacteria within the nasal cavities is all that is necessary to cause a fulminant intracranial infection. This is probably what happened in Case 3. In a third group the osteoma is associated with a pyocele. This occurs in osteomas of the ethmoid more frequently than in osteomas of the frontal sinus. The association of osteoma with mucocoele was known to Virchow,<sup>7</sup> who called the mucocoeles simply cysts. The pus of a pyocele is usually of low-grade virulence and contains no active bacteria; the walls of the pyocele are usually thick and, thus, pyoceles rarely cause progressive inflammation of the meninges or the brain. If, however, the pyocele is unintentionally opened at operation and becomes infected, postoperative meningitis may ensue.

Another complication which may be caused by osteoma is pneumocephalus. The complication occurred in Case 4.

CASE 4.—M. W., white male, aged 49 years. At Christmas, 1946, the family of the patient noticed a change in his personality. He lost interest in everything and did not join the family life. The work in his job was satisfactory. He did not complain of pain. There was no headache. One month ago he suddenly noticed a paresis of his left arm. He was being treated for an allergic sinusitis. He never suffered from frequent sneezing, but he had the habit of sniffing air through the nose. For one year he noticed an



Fig. 4, Case 4.—Osteoma with pneumocephalus, *a*; *b*, air within the brain; *c*, air in the subdural space.

outflow of watery secretion from the nose on stooping over. In the course of the treatment for allergic rhinitis an x-ray picture of the skull was made which revealed conspicuous changes.

At examination on June 24, 1947 the patient was very quiet and the history had to be taken from his wife. However, when he spoke, his answers were proper and correct. He particularly emphasized that he did not suffer from pain of any kind. He realized that his personality had changed and on discussing this point he wept. The general condition of the patient was good; the blood and the eye grounds were normal. The right eyebrow was slightly bulged and percussion at this site revealed a dull sound. There was no tenderness. In both external auditory canals there were marked hyperostoses. The ear drums were normal. The tendinous reflexes were exaggerated, the skin reflexes diminished, but there was no difference between the two sides. There was a slight paresis of the left arm and a central paresis of the left facial nerve. There was no exophthalmos and no eye muscle palsy.

X-ray examination showed a large osseous tumor, the surfaces of which were irregular. The interfrontal septum was separated

from the tumor and particularly the inferior portion was markedly bulged into the left frontal sinus (Fig. 4). The tumor had destroyed the posterior wall of the right frontal sinus and extended into the anterior cranial fossa for about 2 or 3 cm. The intracranial portion of the tumor was cone-shaped, the tip pointing toward the brain. The tumor was firmly adherent to the floor of the frontal sinus for about 3 cm. or more. The distance between the roof of the orbit and tip of the tumor was about 1 cm. the distance between the latter and the anterior clinoid process about 4 or 5 cm. The tumor had apparently destroyed the roof of the ethmoid and extended into the ethmoid. There were no connections between the tumor and the cribriform plate although the tumor extended to the left side above the crista galli. Superiorly the tumor extended more than 1 cm. beyond the upper boundary of the frontal sinus, lateralward the tumor bulged into the frontal squama, but it did not grow together with the latter. At several spots the tumor was adherent to the frontal squama and to the anterior wall of the frontal sinus. Inferiorly the tumor extended to the maxillofrontal suture.

Adjacent to the superior boundary of the tumor there was a large translucent area which extended from the right frontal squama to the right parietal bone. The posterior and inferior boundaries of the area were distinct, the superior and anterior ones indistinct. This area was interpreted as an area of osteoporosis circumscripta (Schüller). The diagnosis was not correct as further observation proved. The large translucent area was caused rather by an accumulation of air within the subdural space. Within the large area there was a smaller area making a deeper shadow on the x-ray films which was caused by an intracerebral pneumocephalus. The pneumocephalus had distinct boundaries and was situated within the brain above and behind the osteoma. It had the shape of a funnel, the tip pointing toward the osteoma. There was a channel filled with air which ran between the tip of the osteoma and the roof of the orbit toward the posterior wall of the frontal sinus. There was no air within the meningeal cisternae or within the ventricles of the brain.

On July 5, 1947, an arcuate incision was made below the right eyebrow and a vertical incision in the middle of the forehead. The supraorbital arch was hyperostotic. The anterior wall of the frontal sinus which was not adherent to the tumor was removed. Above the frontal sinus and close to the midline the boundaries between the tumor and the frontal squama were not distinct. At this site the frontal squama showed an external layer, about 3 mm. in thickness, and a pumice-like diploe; an internal layer could not be

distinguished. The bone was about 1 cm. thick. The bone had either grown together with the osteoma or formed a shell around the tumor. After removal of the surrounding bone, the osteoma was adjacent to the markedly bulged dura. Close to the superior and lateral margin of the tumor there were several cysts containing mucus and necrotic brain tissue. A nick incision was made in the dura and a brain cannula introduced. Immediately air escaped with a puff. Simultaneously 150 cc. of hypertonic glucose were injected intravenously. The brain pressure decreased immediately, pulsations of the brain became visible and blood mixed with air bubbles escaped. The anterior part of the orbital roof was cut off from the rest of the roof and the entire osteoma gently elevated from its bed.

After removal of the tumor the findings were as follows: The inferior portion of the posterior wall of the frontal sinus was present and covered by a normal mucosa. The inferior portion of the interfrontal septum was likewise covered by a normal mucosa and markedly displaced into the left sinus. The nasofrontal duct was patent. It was closed by a piece of fascia lata which was put into the lumen. The floor of the frontal sinus was absent. The cribriform plate was not exposed, but above the remnant of the frontal sinus and the frontal septum there was a defect of the dura, the size of a half dollar. There was a groove in the brain, about 1.5 cm. deep and extending over the midline. The floor of the groove consisted of necrotic and hemorrhagic brain substance and showed the openings of two channels filled with air and extending for about 2 to 3 cm. into the depth of the frontal lobe. The walls of these channels were smooth and there was about 4 mm. of brain substance between the two channels. Since no cerebrospinal fluid had escaped during the operation, one must assume that the subarachnoid spaces had been sealed off and that the pneumocephalon had not reached the ventricles. The groove in the brain was covered with sulfonamide powder, and strips of gauze soaked with penicillin were gently introduced into the pneumocephalon. The arcuate incision below the eyebrow was closed, the incision in the midline of the forehead was left open and a blood transfusion was given.

On July 6 he felt well; he was psychically undisturbed and the paresis of the left arm was markedly improved. On July 8 the highest temperature was 100.8° F. At the operation the superior longitudinal sinus was injured and a tampon was inserted. At the site of the injury there was a balloon-like enlargement of the sinus, the walls of which were very thin. During the dressing, the wall was injured again and oxycel was inserted. On July 17, the temperature was nor-

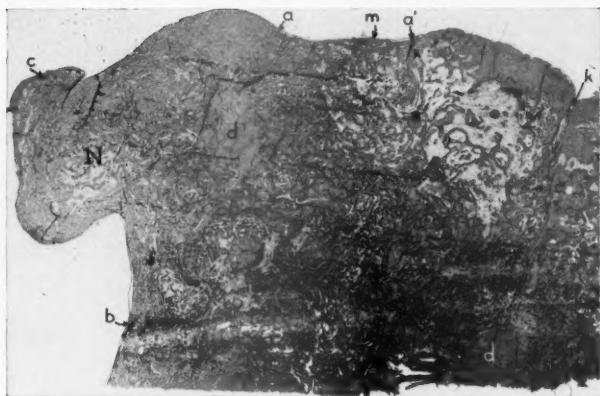


Fig. 5, Case 4.—*N*, exostosis-like nodule; *c*, periosteal compacta. Between *a* and *a*<sub>1</sub> and in *b* the compacta is absent and the cancellous bone reaches the surface of the tumor. *K*, crypt of mucosa; *m*, mucosa; *d*, areas of compact bone consisting of lamellar bone with osteocytes; *e*, area of connective tissue showing metaplastic ossification and invading the periosteal compacta; *x*, spot shown in Fig. 6 in higher magnification.



Fig. 6, Case 4.—*b*, fresh blood in the crypt; *m*, mucosa covered with a ciliated columnar epithelium; *s*, stopline (*Haltelinie*); *L*, lamellar bone of periosteal compacta; *M*, marrow spaces filled with loose connective tissue and capillaries; *o*, osteoclasts; *o*<sub>1</sub>, osteoblasts.

mal and penicillin was discontinued. Altogether he got 18,200,000 units of penicillin intravenously and topically after the operation. The blood count was 3,110,000 erythrocytes, 13,250 leucocytes (neutrophils 71%, eosinophiles 2%, basophiles 1%, lymphocytes 24%, monocytes 2%); hemoglobin 72%. Two Jacksonian attacks, associated with unconsciousness and convulsions of the left arm, were noticed. After the attacks the tendinous reflexes were normal, the abdominal reflexes diminished. On July 19 there were again two attacks, the duration of which were one and nine minutes respectively. Up to this time, he received three blood transfusions of 250 cc. of blood. The blood count was now: erythrocytes 5,480,000, leucocytes 10,150, hemoglobin 75%. Dilantin was administered. On July 25 he again had two attacks. On July 27 there was no fever, no choked disc and no rigidity of the neck. There was a slight facial paresis on the left side, perhaps a positive Babinsky on the left side. Phenobarbital and mesantoin were administered.

On July 29, under local anesthesia the defect of the dura was exposed. It was covered with granulations and the entire area was slightly bulging above the level of the rest of the dura. The defect was covered by fascia lata. The skin incision was closed. At the bridge of the nose and below the eyebrow a small strip of gauze was introduced. The skin suture did not hold entirely. The inferior part of the vertical incision, above the remnant of the frontal sinus, opened again. This opening was allowed to close by granulations. In the process of healing small pieces of fascia lata became necrotic and were expelled. There were no more convulsions and in October the patient was able to resume his work.

*Macroscopic Examination of the Tumor:* The weight of the tumor is about 49 gm. The anterior surface is uneven; the posterior has mottled, small and medium sized nodules projecting from its surface and dipping into the brain substance. The bone of these nodules is white as chalk while the bone of the rest of the osteoma has the yellowish color of normal bone. The inferior surface of the osteoma is firmly grown together with the roof of the orbit. The tumor shows a process which extends into the nasofrontal duct.

*Microscopic Examination:* The tumor consists to a great extent of cancellous bone, the structure of which is different in the center and at the surface of the tumor (Fig. 5). In the center there are thick bone trabeculae which form a network with narrow meshes, occupying a large area of the tumor. The bone trabeculae consist of both lamellar and woven bone, but they do not contain haversian systems. Within the narrow meshes there are connective



tissue and capillaries and there are frequently osteoblasts, laying down new bone and aiming at a sclerosis of the bone. There are no osteoclasts. At other sites of the center there is an accumulation of firm connective tissue containing an occasional accumulation of lymphocytes, a moderate amount of blood vessels and bone trabeculae which consist of woven bone exclusively and are covered by a thick blue *Grenzschleide*. These trabeculae have either no connection with each other or they fuse and form great pieces of acellular (necrotic) woven bone. Toward the surface the amount of connective tissue increases. In contradistinction to the connective tissue within the center of the osteoma, this type of connective tissue is loose and contains a great amount of dilated blood vessels. This type of connective tissue may occupy large areas and contains bone trabeculae, the boundaries of which are covered by osteoblasts or by a blue *Grenzschleide* or show empty Howship's lacunae. Osteoclasts are absent.

The wide-meshed cancellous bone extends frequently up to the surface of the tumor. As other sites, however, the surface consists of a layer of compact bone which is covered by periosteum (Fig. 5). The periosteum consists of a thick layer of connective tissue containing dilated blood vessels. It may or may not be covered by epithelium which is either cubical or consists of one layer of columnar, ciliated cells or is a pseudo-stratified, ciliated, columnar epithelium, indicating its origin in the paranasal mucosa. At several sites, the periosteum lays down a periosteal compacta which may show several blue lines (*Haltelinien*) (Fig. 6).

To summarize, the microscopic findings indicate that the periosteal compacta (Fig. 6) at the surface of the tumor is laid down by the paranasal mucosa which serves as a periosteum. On several sites the paranasal mucosa, characterized by the respiratory epithelium and accompanied by a layer of periosteal compacta, dips deeply into the tumor forming a narrow crypt which is partially filled with blood (Fig. 6). However, the periosteum does not invariably lay down a continuous layer of compact bone. On some places the formation of new lamellar bone takes place between the dilated blood vessels of the periosteum. Thus a compacta is formed which consists of oblong blocks of lamellar bone, loose connective tissue and dilated blood vessels filling the spaces between the blocks. In other words, the compacta has the same appearance as the inner and outer tables of the bones of the vault of infants. When the blocks of lamellar bone grow, the spaces between the blocks become narrower, forming small spaces which run parallel to the lamellae



of the compact bone. Ultimately, the small spaces become filled with newly formed bone and thus a continuous periosteal compacta covers the surface of the osteoma.

The bones of the vault surrounding the osteoma show a normal structure and a normal diploe containing a mixed marrow.

*Comment:* In this case there was a large osteoma of the frontal sinus which destroyed both the posterior wall of the sinus and the dura, and which caused a superficial necrosis of the brain and a large intracerebral and extracerebral pneumocephalus. All of these changes were discovered accidentally when an x-ray film was taken because of nasal allergy. In fact, the clinical symptomatology was extremely poor in this case. The symptoms were: a change of the personality, and a slight weakness of the left facial nerve and the left arm. There were no ocular symptoms except a slight bulging of the right eyebrow. There were no headaches, no neuralgiform pain and no noises within the head. Conspicuous is the absence of headache. This symptom is usually present. Sometimes the patients may have previously had headache but the headache may disappear when the osteoma breaks through the dura.

So far as the pneumocephalus is concerned Teed<sup>4</sup> found among 321 cases only eight cases of osteoma associated with pneumocephalus. The air was extradural in two cases, subdural-extracerebral in four cases and ventricular in two cases. In the presented case the air was discovered in the subdural space as well as within the brain but not in the ventricle; the intracerebral pneumocephalus caused a deeper translucency on the x-ray film than the subdural pneumocephalus because the air formed a thicker layer in the former.

Pneumocephalus is not infrequent in fractures of the base of the skull which create a communication between the air spaces of the paranasal sinuses or the mastoid cells on one hand and the cranial cavity on the other. If the air pressure in the pneumatic cavities is increased, as happens in coughing, sneezing, and even during expiration, the air is pressed through the fracture into the cranial cavity and occupies the space between bone and dura. If there is an additional tear of the dura, the air forms a subdural-extracerebral pneumatocele. In these instances there is usually a simultaneous rhinorrhea cerebrospinalis. Finally, if, by the injury, the cerebral cortex is damaged, the air may invade the brain by a splitting of the brain tissues along the natural layers of cleavage and may even invade the ventricle.

Pneumocephalus in osteoma is caused by the same mechanism: the air pressure in the paranasal sinus must be increased. However, an increase of air pressure in the sinus requires a free communication between sinus and nasal cavity. In the presented case, however, the nasofrontal duct was found to be closed by the osteoma. Although it is difficult to prove that the obstruction of the nasofrontal duct was so firm as to interfere with the passing of air, it seems a fair conclusion that the pneumocephalus developed at a time when there was not yet a complete obstruction of the nasofrontal duct. This would presume that the osteoma had extended into the cranial cavity prior to the complete obstruction of the nasofrontal duct. This however, is not the usual finding in osteomas of the frontal sinus. On the contrary, osteomas usually cause an obliteration of the nasofrontal duct first and then grow into the orbit or the cranial cavity. For this reason it is unusual to find an osteoma of the frontal sinus associated with an accumulation of air in the orbit or the cranial cavity.

If the osteoma breaks through the posterior wall of the sinus and air passes through the nasofrontal duct, an extradural pneumatocele may ensue because the osteoma does not fill up air-tightly the hole in the posterior wall. Cushing<sup>5</sup> had the opportunity to study this condition in a case of a small osteoma of the ethmoid. In his case no sign of communication with the nasal cavity could be made out at operation until the nubbin of the osteoma, projecting into the cranial cavity, was chiseled off. To one side of it there was a minute, thread-like tube of mucosa about the size of a small arteriole. When the patient's nose was held during expiration, a small bubble of air could be forced through the minute channel, showing that it communicated with the underlying ethmoidal cells. In a case of Benjamins and Verbeek<sup>8</sup> the cranial portion of a large osteoma of the frontal sinus was exposed by craniotomy. In front of the tumor a small fistula was discovered in the bone. Unfortunately, no further examination of the fistula was made.

If the osteoma expands, it pierces the dura<sup>6</sup> and opens the subdural spaces. In traumatic pneumocephalus the subdural pneumatocele is usually associated with a rhinorrhea. This is not always so in pneumocephalus caused by an osteoma. In fact, rhinorrhea is not mentioned by Cushing,<sup>5</sup> Carmody<sup>9</sup> or Campbell and Gottschalk<sup>10</sup> although there was a subdural pneumocephalus in their cases. In contradistinction there was rhinorrhea in Cushing's second case and in Armitage's<sup>11</sup> case. In the presented case there was probably a rhinorrhea which, however, apparently disappeared after a

period of time. The probable reason for the variable occurrence of rhinorrhea in pneumocephalus due to osteoma is: in traumatic pneumocephalus there is a sudden tearing of the dura and a sudden opening of the subdural spaces; with osteomas there is a slow and gradual piercing of the dura which is associated with inflammatory changes due to the irritative influence of the osteoma and the invading air. This means the invading osteoma may cause an aseptic inflammation and the formation of adhesions within the subdural spaces. Under these circumstances no rhinorrhea will occur or it will occur for a short period of time only. In addition, the outflow of cerebrospinal fluid through the nose is hampered by an obstruction of the nasofrontal duct.

If the osteoma causes a necrosis of the brain, the air invades the cerebral tissue and finally even the ventricles. In the presented case there was a subdural plus an intracerebral pneumatocele. The ventricles were not invaded.

It is well known that in these instances the air may stay in the skull for a long period of time. In the cases of Passow, Cotta and Bruening the air remained in the brain for 10 to 18 months without extending into the ventricles (quoted by Dandy<sup>12</sup>). In the presented case the air was likewise in the skull for several weeks, perhaps for a few months. In these cases the question arises: Why does the air not flow out through the bone-dural fistula and why is it not resorbed within the subdural spaces? Dandy,<sup>12</sup> Benjamins<sup>8</sup> and others assume that the fistula exerts a valve action allowing the entrance of air but not the outflow of air. We believe that this hypothesis is not necessary. If there is a narrow fistula between the sinus and the cranial cavity, the air cannot disappear entirely from the cranial cavity regardless of whether there is a resorption of air within the cavity or not, because by sneezing and blowing the nose continually new air is forced into the cranial cavity. For this reason the pneumocephalus invariably recurs if by an operation the air is allowed to flow out but the fistula is not closed. This fact is proved by the cases of Cushing<sup>5</sup> and Benjamins.<sup>8</sup>

It is self-evident that these cases can only be managed by surgery. Cushing has suggested a transfrontal osteoplastic craniotomy and a closure of the bone fistula by transplantation of a flap of fascia lata. Almost all cases which were reported have been operated by this method.<sup>10, 11, 13-16</sup> According to Hoover and Horrax<sup>13</sup> the advantage of this method is that the supraorbital ridge can be saved and the cosmetic result is better. This advantage may come into consideration in small osteomas of the ethmoid; it does not come

into consideration in large osteomas of the frontal sinus because in these instances the supraorbital ridge is usually involved. A distinct disadvantage of this method, however, is that it allows only a piecemeal removal of an osteoma of the frontal sinus and does not allow obliteration of the rest of the frontal sinus to be done. For this reason an empty space remains in the forehead; this space may become infected and serve as the source of a late complication.

For this reason in the presented case the operation was done according to the usual technique which is employed in osteomas of the frontal sinus which are not associated with an intracranial complication. In addition to the external frontal sinus operation an obliteration of the nasofrontal duct was done by filling the canal with fascia, and the large defect of the dura was covered by fascia lata. The rest of the frontal sinus was obliterated by allowing granulations to fill in. Thus far, the method has proved successful. So far as we know, only Carmody<sup>9</sup> has performed a similar operation in a similar case. However, in his case the dural defect was not larger than a dime and was not covered by fascia and there was no intracerebral pneumatocele. The cosmetic result in the presented case is not quite satisfactory owing to the large size of the osteoma. The deformity can be repaired by a plastic operation at a later time.

The presented case proves that all osteomas of the frontal sinus, whether they are associated with an intracranial complication or not, can be operated on by an external frontal sinus operation. The mortality rate which was rather high in the past was chiefly caused by surgical injuries of the dura. The risk is still present. The prognosis of a surgical injury of the dura has improved since the advent of the antibiotics, particularly in instances in which the osteoma is not associated with an infection of the sinus. This injury is not uncommon because, in cases in which the osteoma has invaded the cranial cavity, the dura is frequently very thin. For this reason it is not always possible to avoid injury, but certain technical details may help to diminish their frequency. Because there are no definite symptoms indicating whether the osteoma has reached the dura or not, the operation should always be performed with the presumption that the osteoma is adjacent to the dura. The size of the osteoma does not allow any conclusions in this respect. An osteoma of the ethmoid may be small, yet it may be adjacent to the dura. For this reason, the mobilization of the osteoma must be done slowly and carefully. In osteomas of the frontal sinus Benjamins<sup>8</sup> has suggested that the dura be raised from the osteoma in an upward-downward direction so that an injury to the dura be avoided.

## DISCUSSION

Based on microscopic examinations of Cases 3 and 4 we made an attempt to arrive at an opinion concerning the expansion of osteomas. The rate of expansion is very slow, but these tumors do grow (in contradistinction to the almost stationary exostoses) and may even cause dangerous complications.

Bone tissue grows not by partition of the original osteocytes but by the formation of new bone which will be added to the original bone. In osteomas of the paranasal sinuses there are two types of expansion: (1) expansion by increase of the size of the tumor and (2) expansion by the formation of mucocoeles. According to our microscopic examination the increase of the tumor size is due to a metaplastic ossification of the connective tissue and to a deposition of new bone by the paranasal mucosa which serves as a periosteum.

The bulk of the tumor consists of connective tissue which forms a great amount of bone by metaplastic ossification (Fig. 2). This concept agrees with that of Virchow,<sup>7</sup> who states that a fibromatous neoplasm which thoroughly ossifies must be considered an osteoma. Likewise Moenckeberg-Pfeiffer,<sup>17</sup> Fetissof<sup>18</sup> and others believe that the bulk of an osteoma consists of bone, derived from connective tissue by metaplastic ossification. This bone is cancellous and the trabeculae consist of woven bone. The woven bone may be transformed into lamellar bone which does contain blood vessels and is a persistent structure (Fig. 2). The bone trabeculae frequently fuse, forming compact bone which is called secondary compacta (Figs. 1 and 3), if it is situated at the surface of the tumor. When the amount of connective tissue increases, the amount of newly formed bone increases likewise and thus the tumor expands.

The other source for the expansion is the paranasal mucosa which covers the tumor and lays down the periosteal compacta by the activity of osteoblasts (Figs. 1, 5 and 6). The tumor, thus, consists of a spongy core and a solid cortex, the latter being either secondary or periosteal, similar to the cortex of the cranial bones in children. The relationship between the spongy core and the compact cortex varies considerably. In cases 3 and 4, the cancellous bone in the center exhibited an intense formation of new bone and because of the expanding cancellous bone the cortex became absorbed by osteoclasts (Fig. 6) and would eventually have disappeared, allowing the cancellous bone to reach the surface of the tumor.

It is in agreement with the neoplastic character of the osteoma that the expansion of these tumors is entirely irregular. One single

slide may show cancellous bone at the surface at one place, secondary compacta at another place and periosteal compacta at a third place (Fig. 1). Frequently, there are localized spots at the surface of the tumor where both the connective tissue of the mucosa and the connective tissue of the tumor exhibit a particularly strong power of bone formation. This causes the formation of exostosis-like nodules (Fig. 1) consisting of compact bone exclusively or of a core of cancellous bone and a cortex of compact bone. If two nodules of this type are close together, there is a groove, covered by mucosa, between them. If the two nodules grow larger, the groove becomes narrower and finally changes into a slit-like crypt as shown in Figure 5.

As a result of the expansion the osteoma exerts a pressure upon the surrounding bone, causing atrophy and ultimately, destruction of the bone. Thus, the osteoma comes in contact with the periosteum of the orbit or the dura. The resistance of these membranes is great and it is likely that, primarily, these membranes form a new bone which fuses with the osteoma. However, finally these membranes yield to the pressure of the expanding tumor and the osteoma extends into the orbit or the subdural space.

The presented concept does not entirely agree with the usual concept concerning the expansion of osteomas. Four types of osteoma are usually emphasized: the eburnated type, the compact type, the spongy type and the mixed type. The correctness of this classification seems to be doubtful. Frequently the diagnosis is made by a macroscopic examination of the tumor or by a microscopic examination of small pieces of the tumor. Neither method permits conclusions. If large pieces of the tumor had been microscopically examined in all instances, one would likely arrive at the conclusion that the mixed type (osteomas with a spongy core and a compact cortex) is most frequent (Fig. 1 and 5). Very small osteomas, as in the case of Simpson and Williams,<sup>19</sup> may occasionally consist of compact bone exclusively, but this is certainly an exceptional finding in tumors of large size. In fact, Roussy<sup>22</sup> emphasized that "compact" osteomas frequently contain a large amount of cancellous bone and vice versa.

The usual concept concerning expansion of osteomas is that the spongy portion of the osteoma is more recently formed while the compact bone represents an older part of the tumor, that the compact bone forms by fusion of the trabeculae of the cancellous bone.<sup>17, 18, 20</sup> We cannot quite agree with this concept. In the expanding osteoma there is a slow but continual transformation of the compacta as well



as the spongiosa; for this reason it is impossible to state which bone was deposited first. Furthermore, we do not agree with the statement that the compact cortex of the osteoma is exclusively formed by fusion of the trabeculae of the cancellous bone. Although this does occur, resulting in the secondary compacta (Fig. 3), it must be kept in mind that a solid cortex can also be deposited by the activity of the periosteum which forms the periosteal compacta (Fig. 6).

There are certain findings which are significant for the expansion of osteomas as well as for the expansion of osteitis deformans in the sinuses. According to Brunner and Grabscheid,<sup>21</sup> in osteitis deformans the deep layers of the paranasal mucosa likewise produce seams of osteoblasts which, in turn, deposit a layer of lamellar bone. The lamellar bone which is analogous to the periosteal compacta of the osteoma, becomes absorbed by the expanding spongy bone of osteitis deformans; new lamellar bone is deposited which again becomes resorbed and these changes continue until the lumen of the sinus becomes markedly narrowed. Furthermore, in osteoma as well as in osteitis deformans it is not the entire wall of the sinus which bulges into the lumen; there are rather in both diseases exostosis-like nodules which extend into the sinus.

Despite the similarity of these findings there are fundamental differences which sharply distinguish these two diseases. First, the bulk of the newly formed bone is in both diseases cancellous bone, but microscopically the spongiosa is different. In osteitis deformans the bone trabeculae frequently present a mosaic structure; in osteoma the trabeculae consist simply of lamellar or woven bone. In Paget's disease there is an irregular, precipitated transformation of the trabeculae, causing the mosaic structure, and there are many osteoblasts and osteoclasts; in osteoma there is a slow, gradual transformation and few osteoclasts or osteoblasts in any restricted area. Second, osteomas occasionally present pedicles indicating that they have originated from a localized spot in the sinus wall. Paget's disease involves, from the onset, a large area of the sinus wall and, for this reason, there is no formation of a pedicle. Third, Paget's disease frequently forms a hyperostosis interna, particularly of the frontal squama. The hyperostosis may even extend deeply into the cranial cavity; yet it will never pierce the dura. The osteoma not infrequently does pierce the dura (Cases 3 and 4). Fourth, in Paget's disease of the sinuses the rest of the skull is usually involved, occasionally even the rest of the skeleton. These findings are absent in osteoma. Fifth, osteoma occurs particularly in men of young age,



Paget's disease occurs in men as well as women of older age. Considering all of these findings the differential diagnosis between osteoma and Paget's disease should be usually possible.

Concerning the relationship between osteoma and mucocoele it should be borne in mind that the osteoma frequently does not fill up the entire lumen of the involved sinus. Normally some of the sinus cavity persists<sup>20</sup> which is covered by mucosa. If it is in communication with the nose, the mucosa may become infected and become hyperplastic and polypoid. Naturally the mucosa produces secretion which may or may not escape into the nose. If the osteoma interferes with the drainage of the sinus, the secretion remaining in the sinus causes a dilatation of the sinus: a mucocoele. If the osteoma fills up the sinus lumen, a mucocoele cannot form. The mucocoele can expand in all directions except toward the osteoma. The osteoma most frequently expands toward the nose or the orbit. Mucocoeles of the frontal or ethmoid sinuses expand in the same direction if they are not associated with an osteoma. If the mucocoele is caused by an osteoma it must for this reason expand toward the cranial cavity. If, in a case of this type, the osteoma likewise expands toward the cranial cavity, the tumor pushes the mucocoele into the brain<sup>5, 10, 11</sup> which may become infected forming a brain abscess.<sup>15</sup> In the presented Cases 3 and 4 the osteoma was not associated with a mucocoele, but in Case 4 the mucosa, covering the osteoma, presented several small polypi.

#### CONCLUSIONS

1. In the frontal as well as in the ethmoid sinuses small osseous tumors occur which bulge into the sinus and are covered by the sinus mucosa. These tumors do not cause clinical symptoms and at least some of these tumors do not increase in size, certainly not in persons of 50 years or more.
2. An osteoma should be surgically removed whenever it shows a tendency to expand, regardless of ocular symptoms.
3. Osteomas of the paranasal sinuses expand by increase of the size of the tumor and by the formation of mucocoeles.
4. There are no definite symptoms indicating whether an osteoma of the frontal sinus has extended to the dura.
5. The association of an osteoma of the frontal sinus with an accumulation of air in the orbit or in the cranial cavity is not usual.
6. Pneumocephalus caused by osteoma is not always associated with rhinorrhea.

7. All osteomas of the frontal sinus, regardless of whether they are associated with an intracranial complication or not, can be removed by an external frontal sinus operation.

8. The increase in the size of the osteoma is due to a metaplastic ossification of the connective tissue and to a deposition of new bone by the paranasal mucosa which serves as a periosteum.

9. The mixed type of osteoma, the osteoma with a spongy core and a compact cortex, is most frequent.

10. Osteoma of the paranasal sinuses and osteitis deformans of the paranasal sinuses are similar in regard to several microscopic findings; yet there are fundamental differences which sharply distinguish the two diseases.

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LXII

AN EXPERIMENTAL STUDY OF THE TOXIC EFFECTS OF  
STREPTOMYCIN ON THE VESTIBULAR  
APPARATUS OF THE CAT

PART I. THE CENTRAL NERVOUS SYSTEM

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A destructive effect upon the vestibular apparatus is the most important toxic reaction of prolonged therapy with streptomycin. Several investigators have reported disturbances of equilibrium following the administration of streptomycin in divided daily dosage of 1.5 grams or more over periods of 2 to 12 weeks.<sup>1-6</sup> The purpose of this paper is to present some experimental evidence on the site of the damage to the vestibular mechanism.

In a report adopted by the Council on Pharmacy and Chemistry of the American Medical Association, of 543 tuberculous patients who had received streptomycin therapy, vestibular symptoms were observed in 96 per cent.<sup>7</sup> It was suggested in this report that the vestibular dysfunction is due to damage of the vestibular nuclei in the central nervous system, but the evidence to support this suggestion was not given. Brown and Hinshaw<sup>1</sup> expressed doubt as to whether the lesion is in the vestibular end-organ or in the brain. Farrington and his co-workers<sup>4</sup> believe the vestibular damage is centrally located because they found the loss of labyrinthine function to be bilaterally symmetric. Fowler and Seligman<sup>6</sup> state that the mechanism of the otic complications of streptomycin therapy could be either labyrinthine or retrolabyrinthine. Stevenson, Alvord and Correll,<sup>8</sup> in examining the brains of five patients with tuberculosis

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who had become deaf while receiving large amounts of streptomycin, detected liquefaction necrosis in the ventral cochlear nuclei in all five cases. In two of these brains there was a similar type of lesion in the vestibular nuclei. These investigators were able to reproduce the same type of degenerative change in the ventral cochlear nuclei of three dogs which had been given large doses of streptomycin.

In February 1947, one of us (J. W.) in a paper read before the Section on Otolaryngology of the College of Physicians of Philadelphia, suggested that the vestibular lesion is centrally located.<sup>9</sup> This conclusion was based on a study of the vestibular responses of two patients with tuberculosis before, during and after streptomycin therapy.

Mushett and Martland<sup>10</sup> were able to produce disturbances of equilibrium in three dogs by administering large doses of streptomycin. Histologic studies of the cerebrum, cerebellum, medulla and the acoustic, brachial and sciatic nerves failed to show any pathologic alterations. These investigators believe that the toxic changes are in the vestibular end-organs, but they concede that there may be some direct effect upon the cerebellum or other nervous tissue which their studies did not reveal. Molitor and his co-workers<sup>5</sup> found signs of cerebellar or labyrinthine dysfunction in dogs which had received prolonged administration of the drug. Hawkins and Mushett<sup>11</sup> gave large amounts of streptomycin to rabbits, dogs and cats. Vestibular responses to rotation were abolished and ataxia was produced in all three species. There was no return of the labyrinthine response to rotation even after four months following the discontinuation of the drug. Histologic studies in the animals examined were negative for evidence of changes in the nervous system which could be attributable to the streptomycin. These workers suggested that streptomycin may act not only on the peripheral vestibular apparatus but also on the vestibular nerve, the medullary vestibular centers, and the cerebellar and midbrain centers.

We have attempted to locate the lesion or lesions in animals in which the vestibular function was abolished by the parenteral administration of streptomycin sulfate. Three separate methods of investigation were employed: vital staining; surgical destruction of the vestibular nuclei on one side of the brain stem; and histopathologic study of stained sections of the brain.

*Vital Staining.*—The most comprehensive and recent reviews of the existing knowledge on the subject of vital staining have been

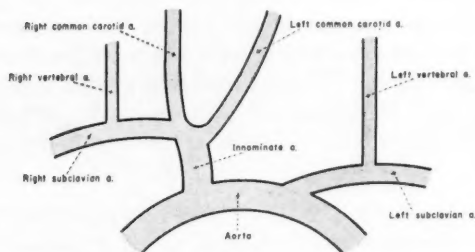


Fig. 1.—Diagram of arterial blood supply in the neck of the cat and the guinea pig.

published by Spatz<sup>12</sup> in 1933 and by King<sup>13</sup> in 1939. The following summary has been drawn largely from King's paper.

In 1900, Lewandowski<sup>14</sup> found that when sodium ferrocyanide was injected in fairly large quantities into the blood stream of rabbits, no significant reaction resulted; but when 1/100 to 1/200 of this amount of sodium ferrocyanide was injected directly into the cerebrospinal fluid, marked nervous reactions with convulsions followed immediately, often resulting in the death of the animal. Goldman,<sup>14</sup> in 1906, repeating these experiments with the acid dye, trypan blue, found that on injecting the dye into the blood stream of an animal, the entire animal stained blue immediately, and the dye could be seen in all the tissues and organs, including the peripheral nerves and the spinal ganglia, but the central nervous system remained unstained with the exception of the choroid plexus. When the dye was injected directly into the spinal fluid, however, staining could be seen in the brain and spinal cord. These experiments suggested that there is a barrier between the blood stream and the tissue of the central nervous system which prevents the passage of certain substances from the blood into the brain and spinal cord. These experiments were repeated by subsequent workers; namely, Schulemann,<sup>14</sup> Rachmanow,<sup>14</sup> Behnsen,<sup>14</sup> and Wislocki and Putnam,<sup>14</sup> who have shown respectively that the neurohypophysis, the tuber cinereum, the infundibulum and the areae postremae also normally stain with trypan blue.

The experimental findings just outlined apply only to normal adult animals. Behnsen<sup>14</sup> has shown that in immature mice (up to about five weeks of age) the central nervous system will stain



Fig. 2.—Brain of normal control cat showing the dye in the meninges and choroid plexus in the ventricle.

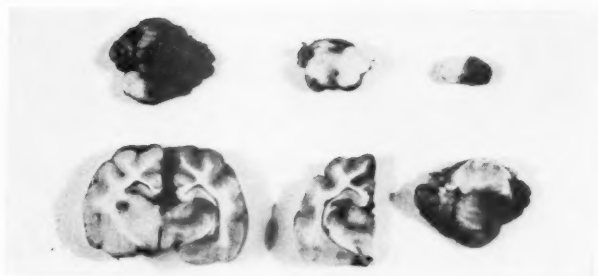


Fig. 3.—Brain and spinal cord of cat having received streptomycin and being vitally stained. The dye can be seen in sections of the brain stem, cerebellum and spinal cord.

with trypan blue more extensively and more intensely than in older mice. Penta<sup>14</sup> confirmed these observations in rabbits and cats. Stern and Peyrot<sup>14</sup> used sodium ferrocyanide, instead of trypan blue, intravenously. These workers could not detect the dye in the brain and spinal fluid of newborn guinea pigs although it could be demonstrated with ease in newborn rats, rabbits, cats and dogs. In the last four mentioned animals, the positive test for sodium ferrocyanide disappeared at about the time the eyes of these animals first opened. The guinea pig is born with its eyes open, a fact which suggests that the nervous system of the guinea pig is more highly developed at birth.

Where the blood brain barrier resides is still a much disputed question. Lewandowski,<sup>14</sup> Goldman,<sup>14</sup> Spatz,<sup>12</sup> Skoog<sup>15</sup> and others believe that the barrier lies in the endothelium of the capillaries of the brain while King,<sup>13</sup> Bouton<sup>16</sup> and others believe it to be in the brain cells; that is, that there is a lack of affinity of brain cells for the trypan blue. King points out that when there is an inflamma-





Fig. 4.—Photomicrograph showing vital staining of the cells of Deiters' nucleus.



Fig. 5.—Photomicrograph showing vital staining of nerve cells of flocculus.

tory or necrotizing lesion of the central nervous system, a change in the brain cells takes place which permits the cells to take up and retain the dye. This change may be biochemical, not morphological, in nature.

All of the animals used in our experiments were healthy adult cats with good vestibular function, as evidenced by the turning test. Three cats were used as controls. One of these, under nembutal anesthesia, received an injection of 20 cc. of a sterile saturated solution of chemically pure trypan blue in 5% glucose into the right carotid artery in the direction of the heart. Two of these cats received 50 cc. of the same solution in the right carotid artery, injected in the same manner, to rule out the question of any toxic action of the dye itself in high dosage upon normal brain tissue. When the dye is injected toward the heart, the meninges of the cerebellum and the brain stem are more deeply stained than when the dye is injected toward the brain. The explanation for this was given by Skoog<sup>15</sup> in his experiments with guinea pigs. On the right side of the guinea pig (and this is also true of the cat) the innominate artery springs from the arch of the aorta and gives rise to the right and left common carotid arteries and the right subclavian artery. The right vertebral artery arises from the right subclavian artery. On the left side the subclavian artery arises directly from the arch of the aorta. The left vertebral artery springs from the left subclavian artery. When the dye is injected into the right carotid artery in the direction of the heart, a high concentration of the dye is carried into the right subclavian artery, thence up through the right vertebral artery, thus first reaching the base of the brain (Fig. 1). Forty-five minutes to one hour after injection of the dye, the three cats were sacrificed with an injection of 25 cc. of 10% formalin into the left carotid artery in the direction of the brain. The brain, spinal cord and temporal bones were immediately removed and prepared for pathological study.

On sectioning the brains and spinal cords, it was noted that there was no macroscopic staining of the nervous tissue, while the meninges and the choroid plexus were stained a deep blue throughout (Fig. 2). Microscopically, there was no evidence of any trypan blue in the nerve cells of any part of the brain and spinal cord. There was also no evidence of any degeneration of the nerve cells.

Five cats received toxic doses of pure streptomycin sulfate. The turning test was done weekly, and the injections of streptomycin were stopped when the vestibular eye response was abolished. One gram of the drug was given daily in three divided doses by the

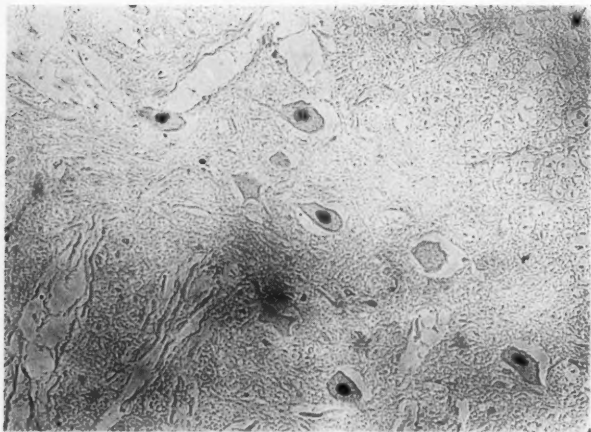


Fig. 6.—Photomicrograph showing vital staining of the pyramidal cells of the anterior horn of the cervical cord.

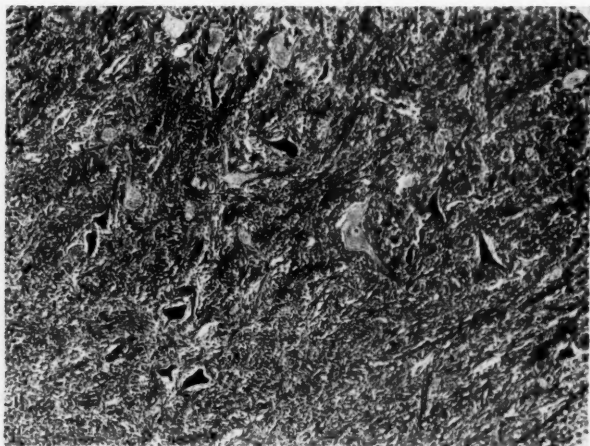


Fig. 7.—Photomicrograph showing diseased cells of Deiters' nucleus stained with phosphotungstic acid.

subcutaneous route. (This dosage is approximately 0.3 gm. of streptomycin per kilogram of body weight and is about eight to ten times the therapeutic dosage for man.) The average total amount of streptomycin per cat was 14 gm. over a period of two weeks. Some of the animals, in this as well as in later groups, became ataxic on the second day after the drug was started and in all, the vestibular responses were absent by the end of the second week. When nystagmus could no longer be elicited by the turning test, each of the cats in this group received 20 cc. of trypan blue solution and they were sacrificed 45 minutes to one hour later with 10% formalin, as previously described for the controls. The brain, spinal cord and temporal bones were immediately removed and prepared for pathological study.

When the brain and spinal cord specimens were sectioned, more or less staining was visible in various parts of the nervous system, the most intense color being noted in the cerebellum and the brain stem (Fig. 3). Microscopically, trypan blue granules were seen in the nucleus of some brain cells and in the nucleus and the cytoplasm of other brain cells in three of these specimens. These findings were confined to: 1.) the Purkinje cells of the cerebellar cortex, most marked in the flocculus; 2.) the dentate and fastigial nuclei; 3.) the medial triangular vestibular nuclei and the lateral (Deiters') nuclei (Figs. 4, 5, 6).

In some animals scattered cells containing trypan blue granules were found in the ventral cochlear nuclei, the tuberculum acusticum, the nuclei of the trapezoid body, and in some of the giant nerve cells of the reticular substance close to the midline. In these same areas the nerve cells were found to be in a pathological state of pyknosis when examined by routine methods of staining; that is, with phosphotungstic acid and cresyl violet (Fig. 7).

Two of the five animals showed a high degree of pyknosis. One of the brain specimens which had shown a lesser number of trypan blue granules also showed a low degree of pyknosis. Another specimen showed pyknosis, but no trypan blue granules were found in the corresponding areas. In one of the animals with marked pyknosis of the Purkinje cells, there was found, in addition, brushlike glial fiber reaction around the dendrites of the Purkinje cells similar to those found by Spielmeyer in typhus.

Since this paper was read, these vital staining experiments have been repeated. The results thus far obtained corroborate the findings described above. In another group of cats the same total daily

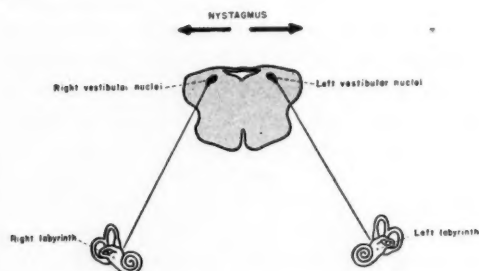


Fig. 8.—Diagram representing vestibular mechanisms under normal conditions.

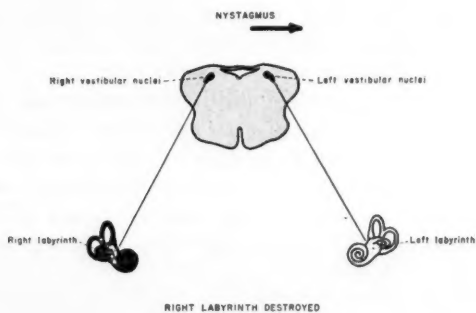


Fig. 9.—Diagram representing situation before compensation has taken place for the destroyed right labyrinth.

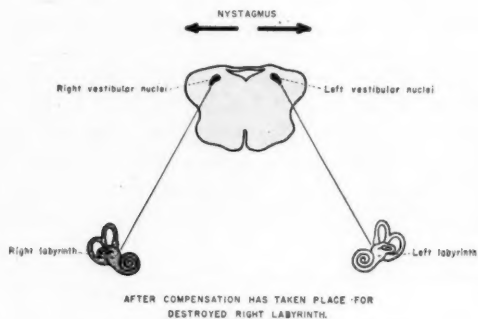


Fig. 10.—Diagram representing situation after compensation has taken place for the destroyed right labyrinth.

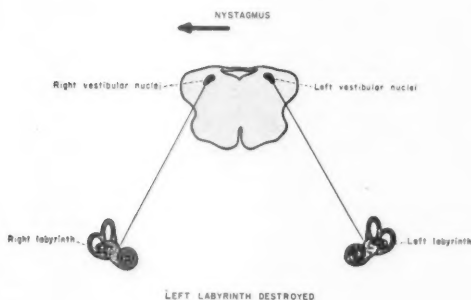


Fig. 11.—Diagram representing situation when the left labyrinth is subsequently destroyed.

dosage of streptomycin (0.3 gm. per kilogram of body weight) was given in one subcutaneous injection every 24 hours for 14 days. These cats lost the nystagmus response to the turning test. In most of the brain sections there were pyknotic changes in the Purkinje cells of the cerebellum, and in a few there were similar pyknotic changes in the vestibular centers of the brain stem, but the brain tissue of these animals did not take up the vital stain. It is believed, therefore, that in order to show the toxic effect of streptomycin upon the vestibular centers by vital staining, the drug must be administered in divided daily doses.

*Surgical Destruction of the Vestibular Nuclei on One Side of the Brain Stem.*—The rationale of this mode of investigation is based largely upon the experimental work of Spiegel and D  m  tr  ades<sup>17</sup> on the vestibular compensatory mechanism. A constant flow of tonic impulses passes through the vestibular nerves and the central portion of both vestibular mechanisms. These impulses arise in the vestibular end organs in the ampullae of the semicircular canals. The tonic impulses flowing through the right vestibular apparatus produce a slow movement of the eyes to the left; that is, the slow component of the nystagmus. Impulses arising from the cerebral cortex cause the eyes to move quickly back to the right. In other words, the tonic impulses in the right vestibular apparatus produce a nystagmus to the right while the tonic impulses flowing through the left vestibular mechanism produce a nystagmus to the left. Both vestibular mechanisms are under normal conditions perfect antagonists so that no nystagmus results (Fig. 8). When, however,

the right labyrinth of a cat is surgically destroyed, there results a nystagmus to the left, this nystagmus representing the action of the normal unopposed left vestibular mechanism (Fig. 9). After several days compensation takes place for the destroyed right labyrinth and the nystagmus disappears (Fig. 10). If, then, the left labyrinth is surgically destroyed, there results a nystagmus to the right (Fig. 11). Since the right labyrinth has already been destroyed, the nystagmus now observed cannot be due to the tonic impulses arising from the nonfunctioning right labyrinth.

Spiegel and Démétriades<sup>17</sup> contended that this nystagmus must be due to tonic impulses arising from the vestibular nuclei on the right side of the brain stem, these nuclei having taken up the function of the destroyed end-organ on the right side. To prove this they destroyed the vestibular nuclei on the left side of the brain stem, before compensation took place for the recently destroyed left labyrinth, and found that the nystagmus to the right persisted, suggesting further that the nystagmus observed was not due to any action resulting from the vestibular nuclei on the left side of the brain stem. Thereupon they destroyed the vestibular nuclei on the right side and the nystagmus immediately disappeared. Thus it may be seen that both vestibular end-organs are physiological antagonists and that the vestibular nuclei on both sides of the brain stem are also antagonistic in action to each other.

Bearing these facts in mind, we felt that if streptomycin in our experimental animals destroyed only the vestibular end-organs on both sides, the surgical destruction of the vestibular nuclei on the right side should produce a nystagmus to the left, the resulting nystagmus being due to the tonic impulses from the unopposed vestibular nuclei on the left side of the brain stem. If, however, streptomycin has either destroyed the vestibular nuclei on both sides or if it has destroyed the vestibular nuclei on both sides and both end-organs, then the surgical destruction of the vestibular nuclei on the right side should produce no nystagmus since the nuclei on both sides of the brain stem have been destroyed previously by the toxic effects of the streptomycin.

In one normal cat, the vestibular nuclei on the right side of the brain stem were surgically destroyed by the following technique: 1.) Anesthesia—a 2% solution of nembutal in physiological sodium chloride solution was injected slowly intravenously until the surgical stage of anesthesia was obtained. This stage was considered reached when pinching of the toe pads of the extended hind leg no longer caused flexion of the limb. 2.) Operative Procedure—under sterile



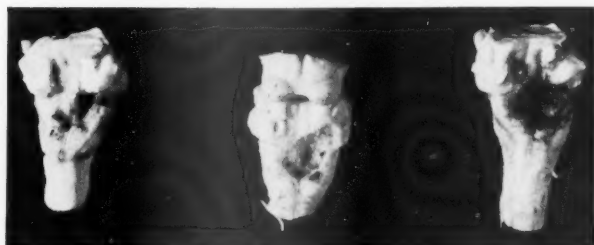


Fig. 12.—Photograph of three cat brain stems showing surgical destruction of the area of the right vestibular nuclei.

conditions, using continuous suction and the electrocoagulating current of a Bovie machine, a craniotomy was performed. The posterior rim of the foramen magnum was removed. The dura was opened and the fourth ventricle visualized by careful tearing of the arachnoid. The vermis was gently lifted and the location of the vestibular nuclei estimated by the usual landmarks. These nuclei were destroyed on the right side with the coagulating current of the Bovie apparatus. The wound was then closed in layers with silk without drainage and a sterile dressing applied. Recovery from anesthesia took place within an hour.

The control cat was observed during the following 24 hours. It was found to lie on its right side with the head down. There was a rapid constant nystagmus to the left, which was considered as clinical evidence that the vestibular nuclei on the right side of the brain stem had been completely destroyed. This cat was then sacrificed with an injection of 25 cc. of 10% formalin, as previously described, and the brain and spinal cord were removed.

Two cats in which the vestibular function had been abolished by the administration of streptomycin, as described previously, were operated upon according to the same technique, and the vestibular nuclei on the right side of the brain stem were destroyed. There was no evidence of any nystagmus during the next 24 hours, nor did these cats assume any definite posture.

The extent of surgical destruction in the brain stems of the control cat and the two cats which received streptomycin is shown in Fig. 12. Serial sections were made on the brain stems of the two cats to which streptomycin had been administered. In one of these

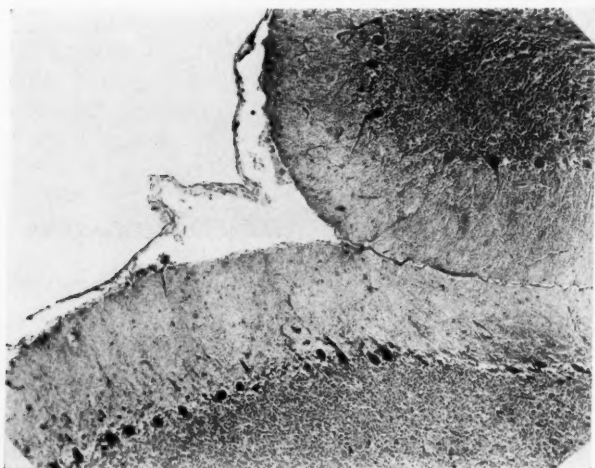


Fig. 13.—Photomicrograph showing diseased Purkinje cells of cerebellum stained with phosphotungstic acid.

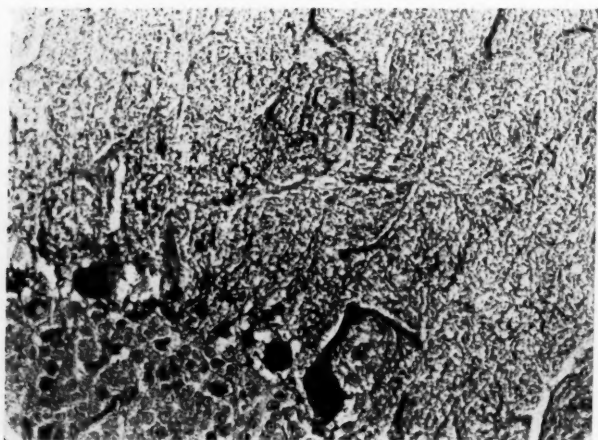


Fig. 14.—Photomicrograph showing diseased Purkinje cells of cerebellum stained with phosphotungstic acid (high power).

it was demonstrated that the vestibular nuclei had been completely destroyed on the operated side. In the brain stem of the second cat a small strip of Deiters' nucleus escaped direct damage from the electrocoagulation.

*Histopathologic Study of Stained Brain Sections.*—One normal cat was used as a control and was sacrificed, under nembutal anesthesia, with 25 cc. of 10% formalin solution injected into the left carotid artery, as previously described. The brain, spinal cord and temporal bones were immediately removed and prepared for study. On examination of sections of various parts of the brain stained with phosphotungstic acid and cresyl violet, there was no evidence of any pathologic change.

Six cats in which the vestibular function had been abolished by the administration of streptomycin, as described previously, were sacrificed in the same manner. The brain, spinal cord and temporal bones were immediately removed and prepared for study. Pyknosis and an increase of glial fibers around the dendrites of the Purkinje cells of the cerebellum were found in four of these animals (Figs. 13 and 14). In one, the degenerative changes were more marked than in the other three animals. There were no pathologic changes observed in the brains of the two remaining cats.

The temporal bones of several of these animals are being examined to determine the presence of a lesion in the peripheral end organ.

#### SUMMARY

Because the prolonged administration of streptomycin frequently causes a disturbance of the vestibular mechanism in man and in certain laboratory animals, we have attempted to locate the site of the injury to the vestibular apparatus by three totally different methods of investigation, using the cat as the experimental animal. Evidence of damage to the central portion of the vestibular apparatus was observed in some of the animals by each method of investigation.

By the vital staining technique, the trypan blue dye was visible grossly in the cerebellum and brain stem in all five animals which had received streptomycin. In three of the five specimens, trypan blue granules were observed microscopically in the nuclei of some of the brain cells in the following locations: 1) the Purkinje cells of the cerebellar cortex, most marked in the flocculus; 2) the dentate and fastigial nuclei; 3) the medial and lateral vestibular nuclei. In

addition, occasional cells containing nuclear trypan blue granules were found in the ventral cochlear nuclei, the tuberculum acusticum, the nuclei of the trapezoid body, and the reticular substance. In the three control cats, there was neither macroscopic nor microscopic staining of the brain tissue, although the meninges and the choroid plexus were stained a deep blue throughout.

Following unilateral surgical destruction of the vestibular nuclei, the control animal showed the proper nystagmus response to the opposite side. In two cats which had received toxic doses of streptomycin, destruction of the nuclei on one side failed to produce nystagmus. This was interpreted as evidence that streptomycin destroys the function of the vestibular nuclei on both sides of the brain stem. However, these findings do not rule out the possibility that the peripheral end-organs of the vestibular apparatus may be damaged also.

Routine histopathologic studies of brain sections stained with phosphotungstic acid and cresyl violet were done on six additional cats which had been given large doses of streptomycin. Pyknosis and an increase of glial fibers around the dendrites of the Purkinje cells of the cerebellum were found in four of the six brains. In the remaining two specimens, no pathologic changes were found.

#### CONCLUSIONS

1. Evidence of damage to the central portion of the vestibular apparatus was obtained when streptomycin was administered to cats under the experimental conditions described.
2. These experimental findings do not rule out the possibility of concomitant damage to the peripheral end-organs of the vestibular apparatus.

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# LXIII

## LARYNGEAL TUBERCULOSIS

OBSERVATIONS BASED ON AN EXPERIENCE OF TWENTY-EIGHT  
YEARS WITH LARYNGEAL TUBERCULOSIS

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Laryngeal tuberculosis is the most common chronic disease of the larynx. The importance of this condition is not always appreciated by the average laryngologist unless he is associated with a sanatorium for the treatment of tuberculosis. This paper is of a practical nature, representing an opinion based on 28 years' experience in the study of laryngopulmonary diseases.

In 1928, we<sup>1</sup> made a study of all patients admitted to the Maryland State Sanatorium from August 1923 to February 1928. In this group, 3,227 patients suffering from tuberculosis were treated. Of these, 500, or 15.5 per cent, showed laryngeal involvement.

We thought it might be of interest to make a recent survey of cases to compare the earlier results with our present findings. Therefore, we have analyzed the patients entering the sanatorium over a ten-year period, namely, from January 1, 1938, to January 1, 1948.

During this period 5,238 patients were admitted to the Maryland State Sanatorium. The larynx was examined in 2,770 cases; it was not examined in 2,468 patients because of an absence of symptoms, a short stay in the hospital, and various other reasons. Of the 2,770 patients examined, tuberculous involvement of the larynx was found in 214 cases, an incidence of 7.7 per cent. This is more favorable than the previous report,<sup>1</sup> where in the period between

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1923 and 1928 the complication was found in 15.5 per cent of all patients.

The decrease in the manifestation of this serious complication is encouraging and is evidently not confined to this locality alone, for Myerson<sup>2</sup> reported an incidence of 10.6 per cent in a study of 10,657 cases in 1944. This improved condition cannot be explained by the type of pulmonary disease of the admitted patients to the sanatorium because in the period from 1923 to 1928 less than 50 per cent of the patients had advanced lesions, whereas in the past few years more than 50 per cent showed far advanced lung lesions. Education has undoubtedly played an important part in reducing the incidence of this complication. In teaching medical students and other members of the medical profession as well, it is advisable to stress the importance of having a laryngeal examination made as soon as a patient is found to have pulmonary tuberculosis.

Since laryngeal complications are always secondary to pulmonary involvement, many cases of beginning pathologic changes can be recognized and treated in the early stages. These lesions are easy to cure if detected before ulcerative changes develop. Furthermore, tuberculous changes often develop within the silent area of the larynx and do not present subjective symptoms.

The inter-arytenoid space, arytenoids, vocal processes, and false cords may have advanced pathologic changes before hoarseness, pain, difficulty in swallowing, or other subjective symptoms occur. An early examination of the larynx with a laryngeal mirror frequently reveals beginning pathologic changes which can be arrested, thus preventing serious complications. Consequently, prophylaxis here is one of the most valuable factors in contributing to improvement in the pulmonary disease, because no patient can recover if he has dysphagia, hoarseness and the cough which inevitably develops if the local laryngeal lesion is unrecognized and untreated.

The number of deaths from tuberculosis has been reduced greatly in the past ten years. For a number of years tuberculosis was the second greatest cause of death but the mortality rate for the past few years has been less than 50 per 100,000. The lessening of the mortality rate no doubt coincides with the reduced number of laryngeal complications. This no doubt shows that by education and early diagnosis many of the patients are able to build up better resistance to tuberculosis; therefore, complications are not so common. Improved general treatment, proper diet, and recognition by the medical profession of the handicaps imposed by possible



complications are all factors which favorably influence the results in these cases.

Pulmonary collapse in selected cases of pulmonary tuberculosis has been one of the greatest advances in the treatment of this disease. It has also reduced laryngeal complications to a considerable degree. Many believe that infected sputum brought up in contact with the laryngeal structures is the most important etiologic factor in the development of laryngeal lesions. Accordingly, if the lung is collapsed and the supply of infected exudate is reduced, the laryngeal involvement becomes less, and certainly the severe cases are prevented. Collapse therapy, therefore, has had a most helpful effect in reducing laryngeal complications.

The diagnosis of laryngeal tuberculosis is not difficult to those associated with tuberculosis sanatoria. However, to the average laryngologist the problem may at times be difficult.

It is now generally admitted that laryngeal tuberculosis is secondary to some pulmonary infection; consequently, voice changes in sanatorium patients readily suggest laryngeal complications. In routine office work, however, making a diagnosis in such cases is more difficult. Hoarseness is usually the first and the most common symptom. This may range from a weakness or huskiness of the voice to complete aphonia, depending upon the pathologic condition. As destructive changes develop, the symptoms are aggravated and there may be dysphonia.

Pain referred to the ear is one of the earliest subjective symptoms. This is a reflex otalgia referred from the superior laryngeal nerve through branches of the vagus.

A cough is usually present. Exudate that is brought up irritates the superficial sensory nerves even though ulcerative areas have not developed. In more destructive ulceration, the act of coughing may be intense and exasperating.

Pain on swallowing is most often seen in lesions of the epiglottis and the arytenoids. Even emollient solutions such as milk may cause intense pain on swallowing if there is much destruction of the mucosa of these structures.

Some patients with edema or infiltration in the glottic airway may develop dyspnea. In a few cases a tracheotomy may be necessary to relieve the symptoms. In our experience, however, a tracheotomy has been required in only two cases.

Men were affected much more frequently than women. In the group reported here 163, or 76 per cent, were men, and 51, or 25 per cent, were women. Evidently the reason males appeared more susceptible is the use of tobacco and alcohol and exposure to more strenuous occupations than females.

The onset of laryngeal involvement is most frequent between the ages of 30 and 50 in men and between 20 and 40 in females; however, it may occur in the extremes of life. Our youngest patient was 18 years of age and the oldest 68.

The relation of occupation to this complication is shown in Table. 2. It is interesting to note that although in our group there were a number of patients who used their voice a great deal, such as ministers and singers, not one of them showed laryngeal lesions. In other words, the use of the voice seemed to play no part in the development of the complication.

Laborers, motormen, farmers and other workers engaged in outdoor occupations showed a greater number of complications than the group of painters, printers, barbers or those who were engaged in some dusty or irritating occupation. This would offer evidence that laryngeal tuberculosis is not a primary lesion but is secondary to the pulmonary condition.

It is at times difficult to differentiate between cases of catarrhal laryngitis and early tuberculosis. As a rule, in patients with catarrh there is some infection found in the sinuses, teeth or tonsils which produces a uniform redness of the mucosa of the pharynx and larynx, and the inflammation clears up when the infected areas are given attention; in tuberculosis there is usually some irregularity in the laryngeal injection and infiltration.

Syphilis has not been common in this series and when present is not difficult to differentiate from tuberculosis since the serologic test for syphilis and general symptoms confirm the diagnosis.

Carcinoma often presents a serious problem in diagnosis. Male patients who are over 45 years of age and are being treated for pulmonary tuberculosis frequently develop lesions on the vocal cords which require considerable observation and study to determine their true nature. In many cases it is necessary to resort to biopsy for a final diagnosis.

Regardless of the number of patients a surgeon has seen, one can never be too sure about the diagnosis. In classes held at the Looper Clinic two patients were presented with extensive pathologic

changes in the larynx. The diagnosis of tuberculosis was made in one and of cancer in the other. However, when biopsies were made, it was found that both diagnoses were incorrect. This emphasizes the importance of biopsy in questionable cases.

The anatomic construction of the posterior laryngeal wall makes it susceptible to invasion by tubercle bacilli. The loose folds of mucous membrane which are in almost constant motion become covered with tubercle-laden sputum. The epithelium is easily irritated and eroded, so that organisms can enter the underlying tissue and tubercles develop. The nature and extent of involvement depend upon the patient's resistance and the course of treatment.

The one characteristic feature of the pathologic changes in laryngeal tuberculosis is the lack of uniformity of the lesion or its location in the larynx. The lesion may be inflammatory, infiltrative, edematous, or of the chronic tuberculomatous type.

However, it is unnecessary in this type of report to go into the detailed pathology of this subject. It has been ably described in many textbooks, especially by Myerson<sup>2</sup> in his excellent book.

Table 3 shows the location of the lesions found in our 214 cases. As illustrated in this table, lesions of the vocal cords were most frequent, with 71 cases. Involvement of the vocal cords and arytenoids was second, with 26 cases. Many patients were admitted in a critical condition with obvious widespread involvement of the larynx, and proper and thorough examination could not be made.

The results of sputum examination are shown in Table 4. In the moderately advanced group, the sputum was positive for tubercle bacilli in 85.7 per cent and negative in 14.3 per cent. In the far advanced group, 99 per cent had positive sputum, and in only 1 per cent was it negative.

Many cases of laryngeal tuberculosis can be prevented; undoubtedly, our most promising work can be accomplished along this line. It is the duty of laryngologists to instruct the family physician in the earlier recognition of these cases. He should be advised of the importance of routine laryngeal examination in every case of pulmonary tuberculosis. Since so much good has been accomplished by educational measures in the recognition and treatment of pulmonary tuberculosis, the same methods should be applied with reference to the complications. Everyone should know that this serious disease is not as hopeless as is generally represented, but that most cases can be cured if recognized in the early stages.

All possible conservative measures should be directed to the correction of pathologic conditions in the upper respiratory tract. Infected sinuses, diseased teeth, and focal infections in the tonsils should be given every possible attention.

It is well known that constant absorption of toxins from these structures seriously affects a normal person; in a patient suffering from tuberculosis, the effects are more dangerous because the system is already overloaded with septic material and any extra handicap may be all that is necessary to overcome the chances of recovery.

Furthermore, irritating purulent secretion has a deleterious action on normal laryngeal mucosa and may be sufficient to injure the epithelium so that invasion by tubercle bacilli is inevitable. Serious consideration should therefore be given to all factors that may have a bearing on the prevention of this complication.

The treatment of laryngeal tuberculosis should be considered under three divisions, namely, general treatment, vocal rest, and treatment of the local lesion.

The general treatment of the pulmonary disease is the most important of all because, as Dworetzky<sup>3</sup> has pointed out, regardless of the type of laryngeal lesion, slight or extensive, there will be little improvement if the patient has a rapid progressive caseous type of lesion with much exudate. Therefore, every effort should be made to arrest the lung lesion. Rest, good food, and the usual hygienic measures of institutional treatment should be given. Pulmonary collapse has been effective in controlling many cases and has certainly been one of the outstanding factors in arresting and preventing the extension of the laryngeal lesion.

All patients should be treated in a sanatorium, if possible, because a carefully regulated plan of general treatment of the pulmonary lesion is most necessary. It is unwise to have patients with active tuberculosis travel long distances to physicians' offices and wait in hot, crowded rooms for treatment. Under such conditions coughing is increased and the strain of travel lowers the patient's general resistance. These unfavorable features are eliminated in sanatorium treatment and the patients can be carefully followed by both the clinician and the laryngologist between whom there should be the closest cooperation.

At the Maryland State Sanatorium, if the patient's temperature is over 99.4° F. and laryngeal complications are found, he is put

to bed and kept on vocal rest. As soon as the resistance is built up somewhat and the temperature begins to subside, cauterizations are started and continued at monthly intervals until the patient is cured.

In all patients in whom tuberculous invasion of the larynx has been discovered, absolute rest of the voice should be instituted. There is little to be gained in telling the patient not to talk; he should be instructed to write everything. Such instructions impress him with the seriousness of his condition and are also important as a curative measure. Unquestionably, many lesions have been cured by silence alone, as has been frequently pointed out, so that whatever other form of treatment may be supplemented, vocal rest should be carried out diligently.

For active treatment of the local lesion we have found the judicious use of electric cautery most beneficial and now employ it in preference to all other methods of treatment. The results have been most gratifying.

The technique of cauterization is simple, the results are sure, and complications are negligible. Cauterization can be carried out easily in an office or at the bedside without inconvenience to the patient. Local anesthesia is employed and the indirect method is advisable; however, the direct method may be used when desired. Early lesions clear up after two or three treatments, and advanced lesions will show definite improvement after a few cauterizations. Even in severe and hopeless cases the cautery is of great value as a palliative measure to relieve pain and coughing.

In only three cases was it necessary to inject or resect the superior laryngeal nerve. These patients received temporary relief from intractable pain but eventually died.

Fourteen patients were treated by sulfanilamide powder insufflation which was used for the relief of pain from widespread laryngeal destruction. Relief was definitely obtained in six cases, the pain being reduced and the exudate diminished. Two patients were unimproved, and six patients died.

Table 5 shows:

1. Only two cases of laryngeal tuberculosis occurred with minimal lung involvement. The larynx of one of these patients was cauterized and improved; the other did not require cauterization and improved.

2. Of the 14 patients with moderately advanced pulmonary disease, the throat was cauterized in 10, or 72 per cent, and not cauterized in 4, or 28 per cent.

Of the patients whose throats were cauterized, 7, or 50 per cent, were improved, and 3, or 21.4 per cent, were unimproved. There were no deaths in this group.

Of the patients whose throats were not cauterized, 4, or 28.6 per cent, were improved under ordinary sanatorium care, including vocal rest or absolute silence. There were no unimproved or fatal cases in this group.

3. Of the 198 patients with far advanced lung involvement, the throat was cauterized in 115, or 58.1 per cent, and was not cauterized in 83, or 41.9 per cent.

Of the patients whose throats were cauterized, 69 or 34.8 per cent, were improved and their lesions healed; 12 or 6.1 per cent, were unimproved; 29, or 14.6 per cent, died. In this last group the cauterization was done more for a psychic reason or to relieve temporarily the severe pain associated with swallowing, particularly in patients with involvement of the epiglottis. The outlook for this group was absolutely hopeless on admission.

Of the patients whose throats were not cauterized, 13 were improved and their lesions healed under ordinary sanatorium care, including vocal rest or absolute silence; 21 or 10.6 per cent were unimproved; 48 or 24.3 per cent, died. Three per cent of the patients with far advanced cases left the institution before a follow-up report could be made on the laryngeal lesions.

The rather large percentage of unimproved patients and deaths in the group whose throats were not cauterized can easily be explained by the fact that the majority of patients with far advanced disease are toxic. In them the disease runs an active course, there is a hectic temperature, and cautery treatment is contraindicated.

Of the 48 who died without having the throat cauterized, the majority were in the sanatorium for only brief periods of time. The comparative results of those whose throats were cauterized with those whose throats were not cauterized are rather striking. It was definitely noted in far advanced cases, where the prognosis was always grave, that the cautery exercised a favorable influence on the lungs and on the general condition of many patients.

The laryngeal lesion is essentially a cellular infiltration. This infiltration is avascular, with a tendency to rapid destruction of the

central cells. The beneficial action of the cautery is attributable more to the revitalization of the tissues by induced hyperemia than to destructive action of the heat. The development of granulation tissue and the formation of new blood vessels following the sloughing of the cauterization area account for the good results. The great advantage of using electrocautery is that its action is limited to the diseased area.

Since electrocautery will in almost every instance accomplish good results it should be considered the best method for the treatment of laryngeal tuberculosis. The treatment should be undertaken only in patients in whom there is no fever or just a slight elevation of temperature, except in patients with urgent symptoms that demand intervention.

Every case should be studied carefully, for indiscriminate cauterization will not accomplish results. It is most important that there be the closest cooperation between the internist and the laryngologist when treating these patients. A patient who is admitted with fulminating general symptoms and elevated temperature should be kept in bed and the general resistance built up before cauterizations are started, for if there is not sufficient resistance to overcome some of the general effects, one cannot expect the laryngeal lesion to be cured by any form of treatment.

However, we feel that in any reasonably early case the chances of cure are good. The prognosis of laryngeal tuberculosis should be more promising and the percentage of the complicated cases grow less as time goes on. We should be able to get these patients in time for effective treatment, for this will also help to reduce the general mortality of tuberculosis.

In the past few years there has been a definite reduction in the number of laryngeal lesions requiring cauterization. This is evidently the result of education and earlier recognition of these cases, better general treatment, collapse lung therapy, and a lessened incidence in the number of these cases. Our latest report showed only 7.7 per cent with laryngeal complications.

The use of streptomycin and the sulfonamides has proven so satisfactory that their importance cannot be overemphasized in the treatment and prevention of this complication and no doubt as their general use is more widely employed, the incidence will be further reduced. Such treatment has undoubtedly played a part in the reduction of cases requiring cauterization.



In the earlier work at the sanatorium, it was not unusual to cauterize from 20 to 25 patients per month. At the present time, the average runs from two to five during the same period. This is very encouraging as it shows that these serious laryngeal complications are under control and there is great promise of continued improvement.

#### SUMMARY

1. During the past 25 years much progress has been made in education, diagnosis and the treatment of tuberculosis.

As laryngeal tuberculosis is always secondary to lung involvement, the disease should be treated as a laryngopulmonary infection. No laryngeal complication can be cured if the patient has a soft exudative lung lesion, with little resistance to overcome the general infection; therefore, every effort should first be directed to the treatment of the general disease.

2. Pulmonary collapse has been a marked factor in reducing laryngeal complications as well as having beneficial effects on the lung lesion. These procedures lessen the chances of infected sputum being brought up and deposited on the laryngeal mucosa to cause contact invasion of tubercle bacilli.

3. Infected sputum is the most common cause of laryngeal tuberculosis, but organisms may enter by way of the lymph and the blood streams.

4. A thorough examination of the larynx should be made in all cases of tuberculosis, as soon as a pulmonary lesion has been discovered.

5. Slight congestion, dryness and tickling sensations of the larynx should promptly receive attention, as such symptoms often indicate early invasion of the larynx.

6. Laryngeal tuberculosis occurs at all ages, but the majority of cases are found between 20 and 50 years of age, with males predominating.

7. Laryngeal tuberculosis has no relation to occupation.

8. All pathologic conditions in the upper respiratory tract, such as deviated septum, sinusitis, hypertrophied turbinates and infected tonsils should be corrected.

9. Nontuberculous laryngitis, colds, tonsillitis and excessive coughs in tuberculous patients should receive prompt attention, as

conditions leading to superficial loss of epithelium open the way to infection by the sputum.

10. The frequency of involvement of various parts of the larynx is directly proportional to exposure, irritation and functional activity.

11. Laryngeal tuberculosis has never been a promising field for medicinal therapy regardless of the method of treatment. Many different drugs have been used and many local applications have been tried, most of which have been abandoned, especially caustics and irritants. However, penicillin, sulfonamides, streptomycin and newer drugs may prove to be of value.

12. The results of cautery used sporadically in the Maryland Tuberculosis Sanatorium until August 1923, were so impressive and encouraging that we felt its continued and increasing use was our best form of treatment.

13. Of all our patients with laryngeal lesions with moderate lung involvement treated by electrocautery, 50 per cent were improved and the lesions healed, and 58.1 per cent with far advanced lung involvement were improved and the lesions healed.

14. Cautery treatment in many patients exercised a favorable influence on the lungs and on the general condition. No bad results were encountered.

15. Cauterization in all patients has been done under local anesthesia by the indirect method at about monthly intervals.

16. Results obtained by electric cautery treatment indicate without doubt that tuberculosis of the larynx is curable, if treatment is started reasonably early.

17. In all suspicious cases we advise vocal rest or absolute silence. While active laryngeal tuberculosis does not have any tendency toward spontaneous healing, it is surprising with what rapidity some incipient lesions with slight infiltration will clear up as the result of absolute silence. Therefore, regardless of what method of treatment is added, silence is imperative in all cases.

18. We still feel that electric cautery continues to be the best method of treatment of laryngeal tuberculosis at the present time.

19. The revitalization of the tissues by induced hyperemia and the development of granulation tissue with formation of new blood vessels account for the good results obtained by the cautery.

20. Elevation of temperature (high degrees), marked asthenia and high blood pressure are contraindications in using cautery, although in patients in whom serious symptoms (severe pain, difficulties of swallowing) demanded alleviation, we did use cautery to bring temporary relief.

21. In using electrocautery, one thing should be particularly and strongly emphasized and this is the condition of the lungs. No laryngologist should undertake electrocautery treatment without cooperating with or being guided by a clinician. Indiscriminate use of cautery in unsuitable cases will do more harm than good and the method of treatment itself will be brought into disrepute.

22. It is encouraging to note that the number of cases requiring cauterization in the past few years has been steadily diminishing. When I first started at the State Sanatorium 28 years ago, from 20 to 30 patients per month required this treatment, while today only four or five per month are cauterized.

23. This is probably due to the smaller number of cases found.

24. In our recent survey, we found an incidence of only 7.7 per cent of laryngeal complications, compared with 15.5 per cent of our cases in 1928. Dworetzky<sup>4</sup> found an incidence of 25.6 per cent in 1914. This shows how much less these complications have become. This holds much promise for the future and we can be optimistic of continued progress in preventing these complications.

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TABLE 1.—AGE DISTRIBUTION

AGE	MALES	FEMALES	TOTAL
10-20	3	2	5
20-30	17	18	35
30-40	48	18	66
40-50	51	10	61
50-60	35	1	36
60-70	9	2	11
TOTAL	163	51	214

TABLE 2.—RELATION OF OCCUPATION TO LARYNGEAL TUBERCULOSIS.

OCCUPATION	NUMBER OF CASES
Physicians, dentists, nurses, etc.	5
Students, teachers	0
Salesmen, saleswomen	5
Dusty occupations	48
Open-air occupations	78
Clerks, stenographers	27
Housewives	31
Sedentary occupations	18
Voice users	0
No occupations	2
TOTAL	214

TABLE 3.—LOCATION OF LESIONS.

LOCATION OF LESIONS	NUMBER OF CASES
Vocal cords	71
Vocal cords and arytenoids	26
Epiglottis, arytenoids and aryteno-epiglottidean folds	17
Arytenoids only	17
Epiglottis and vocal cords	17
Epiglottis only	14
Widespread laryngeal involvement	11
Location not stated	11
Epiglottis, vocal cords and arytenoids	9
Tongue, without laryngeal lesion	9
Tongue, tonsils with laryngeal lesion	5
Posterior wall and interarytenoid sulcus	3
Palate, without laryngeal lesion	2
Tonsils, without laryngeal lesion	2
TOTAL	214

TABLE 4.—SPUTUM EXAMINATIONS.

EXTENT OF PULMONARY LESION	POSITIVE	NEGATIVE	TOTAL
Minimal		2	2
Moderately advanced	12	2	14
Far advanced	196	2	198
TOTAL	208	6	214

TABLE 5

PATIENTS TREATED BETWEEN JANUARY 1938 AND JANUARY 1948

EXTENT OF PULMONARY LESION	THROATS CAUTERIZED				TOTAL
	IMPROVED & HEALED	UNIMPROVED	DIED	NO REPORT	
Minimal	1				1
Moderately Advanced	7	3			10
Far Advanced	69	12	29	5	115
THROATS NOT CAUTERIZED					
Minimal	1				1
Moderately Advanced	4				4
Far Advanced	13	21	48	1	83
TOTAL					<hr/> 214

## LXIV

### STREPTOMYCIN IN TREATMENT OF LARYNGEAL TUBERCULOSIS

BEN T. WITHERS, M.D.

HOUSTON, TEXAS

Because of the dearth of knowledge in the early summer of 1947 regarding the use of streptomycin in treatment of laryngeal tuberculosis, this one year's study was begun.

The patients studied were all bed patients in the Houston Tuberculosis Hospital, a teaching affiliate of Baylor Medical College, operated by the City of Houston. Since there is an acute hospital bed shortage, particularly for tuberculosis patients, the census of this institution is made up principally of patients with advanced pulmonary tuberculosis, either unilateral or bilateral. This fact limited the observations to patients with laryngeal involvement frequently of long standing and usually of a very severe type. Another limiting factor was the cost of streptomycin. Since the majority of patients needing the drug could not afford to buy it, charitable individuals and institutions were relied on to furnish money for the drug. There were no large grants forthcoming; so each case was an economic problem unto itself. Therefore the number of patients studied in this series is only 12. The number is too small to draw statistical conclusions; however, it is hoped that the observed trends, when added to the accumulating work of others on this problem, will be of some value.

The streptomycin purchased and administered was that manufactured either by Lilly or by Merck. A 6B Western Electric audiometer was used for all audiograms. No sound-conditioned room was available for audiometry but the acoustic environment was essentially constant for a given case and any gross changes in hearing would certainly have been reflected in the threshold curve. A modification of the Kobrak caloric test was employed and recorded according to the method of Fowler, Jr.,<sup>12</sup> Lyman<sup>20</sup> and Cody.<sup>4</sup> A 10-cc. syringe and a No. 16 gauge needle were used to inject 5 cc.

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A dissertation presented to the Board of Graduate Studies of Washington University, St. Louis, Mo., in partial fulfillment of the requirements for the degree of Master of Science in Otolaryngology, May 1948.



of tap water at 40° F. into the external ear canal. The timing was begun at the same instant with the injection and stopped when nystagmus was observed (patient sitting with head in upright "face forward" position) by careful scrutiny of the corneoscleral junction with a beam of light reflected from a head mirror. The nystagmus was then observed with the patient in the head upright "face up" position. In each case the direction, type and amplitude were recorded for testing of both ears. A General Electric X-Ray Solution Fahrenheit thermometer was used for temperature readings. The standard procedure for the Romberg test was used in addition to the Kobrak caloric test as an assay of vestibular function.

The patients studied were those adults with pulmonary tuberculosis who had clinical evidence of hoarseness or aphonia, and in some cases odynophagia (painful swallowing). Both white and colored, male and female patients were studied. The patient was given a routine otolaryngological examination, notations were made and a sketch of the larynx as seen by mirror examination was recorded. An audiogram was made and Kobrak caloric test and Romberg test done. No regime of voice rest was instituted. The patients were started on 1 gm. of streptomycin divided into two doses and given intramuscularly twice daily: at 6:00 a.m. and 6:00 p.m. No aerosol streptomycin treatment was given. In addition to the streptomycin, every other patient (total of six) was given 10 mg. of thiamine hydrochloride three times daily by mouth. No facilities for the study of blood levels of streptomycin or of sensitivity of the tuberculosis organisms to the drug were available. The patients were observed throughout treatment for therapeutic effects and possible toxic manifestations. At the end of 90 days of therapy, the above tests and observations were repeated and recorded. No systematic follow-up as to permanence of results has been possible. Sufficient time has not elapsed since the last patients finished treatment. However, none of the first patients treated has shown signs of recurrence of laryngeal disease to date. No controls were used, since the course of tuberculous laryngitis in the absence of specific treatment is well known, nor was any attempt made to record the effect of streptomycin therapy on the clinical course of the pulmonary tuberculosis; such an investigation is not within the scope of this study.

The subject to be developed will proceed according to the following outline: (1) dosage of streptomycin; (2) route of administration; (3) trends in therapeutic value, including thiamine as an adjunct; (4) toxicity of streptomycin; (5) discussion; and (6) summary.

The optimum dosage of streptomycin in treatment of laryngeal (or other) tuberculosis has not yet been definitely determined. Figi et al<sup>11</sup> in one case of laryngeal tuberculosis reported in March 1946 used 0.8 to 1.0 gm. per day intramuscularly, divided into eight equal doses, for 45 days, in conjunction with the local administration of streptomycin solution by nebulization. Hinshaw and Feldman<sup>6</sup> advised in November 1947 the use of 1.0 to 2.0 gm. per day "under most conditions" in divided doses, given every six hours intramuscularly for periods of three or four months. A joint United States Army, Navy, Veterans' Administration<sup>1</sup> report, released in December 1947, advocated the use of 1.8 gm. per day divided into six 0.3 gm. doses, to be given at four-hour intervals for 120 days in treatment of pulmonary tuberculosis. Fowler, Jr. and Seligman,<sup>13</sup> reporting early in 1947, outlined otic complications in various tuberculous patients who had received 3.0 gm. of streptomycin for a total dosage of 10.0 to 49.0 gm.

The Council of Pharmacy and Chemistry of the American Medical Association<sup>7</sup> announced late in 1947: "In general, acute infections may be treated with a total dose of two or three grams (of streptomycin) daily, given in divided doses three to four hours apart . . . In chronic or less severe infections a daily dose of one to two grams may be sufficient to control the disease."

It will be noted from the above references and dates that at the time our study was begun information on dosage and treatment regime for laryngeal tuberculosis per se was scant. With the hope that a dosage adequate for therapeutic purposes, yet small enough to minimize toxic effects could be found, a dosage of one gram per day was decided upon. Feldman, Hinshaw and Karlson<sup>10</sup> had found in their animal experiments that, in guinea pigs, administration of streptomycin twice daily was adequate to control tuberculous infection. They stated in regard to human cases: "It would appear advisable at present (May 1947) to administer streptomycin at frequent intervals in cases of tuberculosis. However, large doses are well tolerated by human beings."

In view of their animal experiments and the latter part of the above statement, it was decided that for our patients the one-gram dosage should be divided into two equal amounts and administered by intramuscular injections at 12 hour intervals. Such regime did not interfere materially with the rest and comfort of the patient. This fact is of some importance in consideration of any therapy for a tuberculous patient.

The most effective route or combination of routes of administration of streptomycin is another problem to be settled in treatment of laryngeal tuberculosis with streptomycin. In the case of Figi et al<sup>11</sup> the drug was used both by intramuscular injection and locally by the nebulization of the drug. This patient was apparently completely cured. Hinshaw, Pyle and Feldman<sup>18</sup> reported successful treatment of ten patients with tuberculous ulcerative lesions of the hypopharynx, larynx and the tracheobronchial tree with a similar combined treatment utilizing both routes. Black and Bogen<sup>2</sup> had discouraging results when the aerosol route alone was utilized without intramuscular injection in treating laryngeal tuberculosis. However, the work of Steenken, D'Esopo and Wolinsky<sup>23</sup> and others indicates that the intramuscular route alone might prove satisfactory in treating this extrapulmonary complication of tuberculosis. They state, "When streptomycin is administered every four hours in a total daily dose of 1.8 to 2.0 grams, the average concentrations . . . in the tracheobronchial tree are much greater than those which completely inhibit the growth of tubercle bacilli in vitro."

Black and Bogen corroborated this laboratory finding by therapeutic results in a series of an additional 11 patients on whom the intramuscular route alone was used but with the total daily dose being only one gram per day. They reported four of the 11 cured and the remaining seven definitely improved. Our results compare favorably with their findings.

From the current literature one might sum up the thinking in regard to the route of administration as follows: The use of streptomycin locally by spray, aerosolization or nebulization without intramuscular administration is not satisfactory. A combination of the two methods is effective. Streptomycin given only intramuscularly seems to give improvement in all cases and cure in some. If the percentage of cures using only the intramuscular route could be proven high enough, this technique would be the most logical. The patient would have neither the expense of the apparatus and oxygen for nebulization, nor the bother of administration of the treatment at frequent intervals throughout the period of therapy. Having chosen the dosage, as indicated above, for our patients, the intramuscular route alone was decided upon: one gram per day divided into two equal doses administered intramuscularly at 6:00 a.m. and 6:00 p.m. with no local therapy.

*Therapeutic Value of Streptomycin.*—As stated before, one would not attempt to offer the results of any treatment of 12 patients as definitive proof. However, unmistakable improvement in

all cases and clinical cure of laryngeal tuberculous lesions in 10 of 12 cases is an encouraging observation and speaks in favor of streptomycin as administered in our small series. This observation is enhanced when one recalls the importance to the prognosis of ridding the patient of pain on swallowing—so often a bar to the all-important high caloric, high vitamin diet in the general successful management of a tuberculous patient. Before detailed consideration of results, a brief review of the opinion on tuberculous laryngitis untreated by streptomycin is in order. Particularly is this necessary since we used no controls in our study. (Aside from other considerations, we believed that every patient for whom streptomycin could be procured should have benefit of the treatment.)

Thomson and Negus<sup>24</sup> stated in regard to tuberculosis: "It is well to remember that the presence of a laryngeal lesion considerably darkens the prospect of recovery in any case of pulmonary tuberculosis . . . Of 477 cases of laryngeal tuberculosis under our care in a sanitarium no less than 70.5 per cent were dead within a few years . . ."

Speaking along the same line of thought, Chevalier Jackson<sup>19</sup> stated: "The prognosis of laryngeal tuberculosis is closely interlocked with the prognosis of the accompanying pulmonary tuberculosis. The advent of the laryngeal lesion is regarded by all phthisiologists as adding seriously to the prognosis of the pulmonary disease; yet it is an unquestioned fact that if the pulmonary lesions heal, the prognosis of the laryngeal tuberculosis is good."

Even with the attempts at specific therapy for tuberculous laryngitis used before the advent of streptomycin, results were very unsatisfactory. Black and Bogen<sup>2</sup> reported on 30 patients with tuberculous laryngitis treated at Olive View Sanitarium (California) over a period of one year with only ultraviolet radiation and cautery, voice rest and general sanitarium care. Results were: "only two appeared healed and six improved, with twenty-two unimproved or worse." It appears to be generally accepted that the occurrence of tuberculous laryngitis is a sign which makes the prognosis more grave. The more extensive the pulmonary involvement, the graver the prognosis for a given patient developing this lesion. We believe streptomycin will cause a re-evaluation of this whole trend of thought.

As previously noted, the patient of Figi et al<sup>11</sup> treated with streptomycin (by intramuscular injection and aerosol route) was completely cured. Prompt healing was also reported from the Mayo Clinic a year later in cases of ulcerative lesions of the hypopharynx,

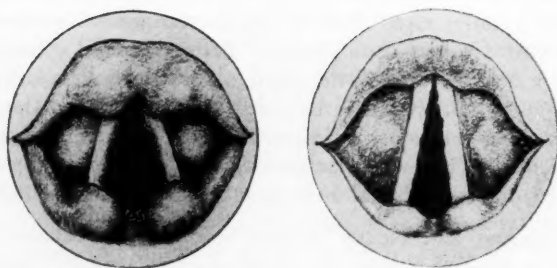


Fig. 1, Case 3.—Showing marked edema of the epiglottis and aryepiglottic folds with ulceration of the interarytenoid area and both true vocal cords.

Fig. 2, Case 3.—Showing disappearance of all edema, after treatment, and scarring at the site of deepest ulceration.

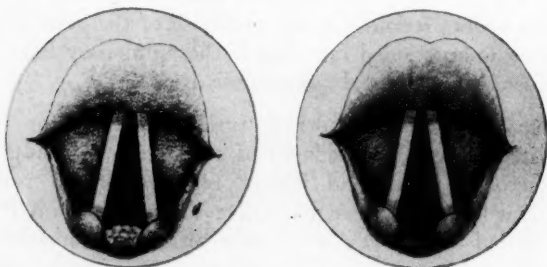


Fig. 3, Case 5.—Showing "piling up" of the interarytenoid area. No lesion or edema elsewhere.

Fig. 4, Case 5.—Showing lesion completely healed.

larynx and tracheobronchial tree by Hinshaw, Pyle and Feldman<sup>18</sup> who used the same or similar technique. Black and Bogen,<sup>2</sup> who treated 34 patients having tuberculous laryngitis locally, as well as by injection, and utilized various agents, found streptomycin to be "by far the most effective treatment so far known."

The results in our series of 12 patients treated with one gram of streptomycin given daily intramuscularly were equally encouraging. All 12 patients showed marked improvement, none remained the same, none grew worse. In ten patients the laryngeal lesion was considered completely cured. By this is meant that all edema subsided and ulcerations and granulations either disappeared or were replaced by scar tissue. One patient was improved but signed a release and left the hospital before we could complete the study of his case. Another patient, whose lesion consisted of granulations posteriorly on the right true vocal cord and a tuberculoma the size of a small olive on the interarytenoid area, was not completely cured. The granulations on the vocal cord healed and the tuberculoma diminished in size by two thirds but did not entirely disappear. In most of the patients hoarseness disappeared within the first 15 days of treatment. Two patients who had complete aphonia at the beginning of treatment and a third who had the large tuberculoma ended up with slight huskiness but a good usable voice. The residual functional impairment was thought to be due in the first two cases to the fact that when the deeply ulcerated areas healed, a depressed scar was left. In the third patient residual husky quality to the voice was due to the tuberculoma which remained one third of its original size. Patients with odynophagia lost this symptom within the first two weeks of treatment, usually within the first week to ten days. The accompanying figures (Figs. 1-8) illustrate the pretreatment and posttreatment appearance of the larynx in four cases. Two cases are shown in which the clubbing of the arytenoids, "piling up" of interarytenoid area and ulceration, if any, have completely cleared. Two cases are shown in which the very deep ulceration of the true vocal cords has left smooth depressed scars after healing.

In six cases, thiamine hydrochloride, 10 mg., three times daily by mouth, was given after meals, concurrently with the streptomycin therapy. The purpose of thiamine administration was to see if the healing process could thereby be enhanced or accelerated. Cody<sup>6</sup> has pointed out that since the daily requirement of thiamine is increased in chronic tuberculosis, "thiamine deficiency is one of the etiologic factors of hypertrophy of the arytenoids in tuberculosis

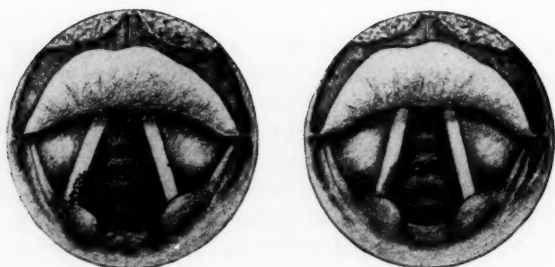


Fig. 5, Case 2.—Showing deep posterior ulceration of the right vocal cord and minimal "piling up" of the interarytenoid area.

Fig. 6, Case 2.—Showing a smooth scar at the site of ulceration and disappearance of the interarytenoid lesions.

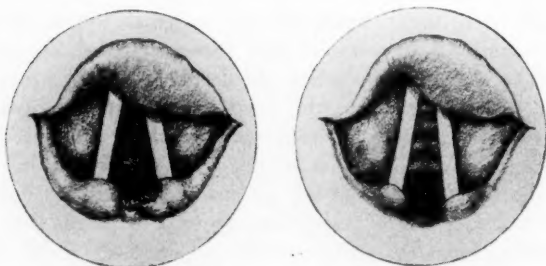


Fig. 7, Case 7.—Showing clubbing of arytenoids with ulceration of the left one and of the interarytenoid area.

Fig. 8, Case 7.—Showing complete healing and disappearance of edema.



of the larynx." He reported a decrease in size of the arytenoids in these cases by the use of 30 mg. of thiamine hydrochloride daily, but not a cure of the laryngeal lesions. The six cases in which thiamine was used in conjunction with streptomycin therapy in our group did not show any detectable difference in course of healing than the other six. One can make no conclusion from so small a number. It is possible, however, that on streptomycin therapy the beneficial effects of thiamine were masked for a reason that readily comes to mind. Most of the patients on streptomycin began to eat better very early in the treatment.

Whether this was due solely to disappearance of odynophagia or to the psychological improvement of outlook because of the drug, one cannot say. In any case it is logical to assume that increased dietary intake of the hospital's vitamin-rich foods would tend speedily to restore vitamin balance in the patient.

In Cody's patients the improvement must have been due to the specific effect of the thiamine hydrochloride rather than to any effect of stimulating the appetite, because it has been independently observed by Wassersug,<sup>25</sup> ". . . that in the presence of an active tuberculous lesion neither vitamin B, nor insulin, exerts an appreciable effect in stimulating appetite."

Hence it would seem that streptomycin may prove doubly beneficial: by specific effect on the laryngeal lesion, as well as by allowing an increased high vitamin dietary intake (even without thiamine supplement). Some might counter this statement by arguing that the labyrinthine toxic effects (dizziness, vertigo, nausea and vomiting) of streptomycin would preclude such improvement. As will be pointed out, on the regime which we followed toxicity was practically nil.

In summing up the therapeutic value of streptomycin treatment of laryngeal tuberculosis in twelve cases, one can say only that the results were very encouraging. The use of thiamine hydrochloride simultaneously in six cases made no discernible difference.

*Toxicity of Streptomycin.*—Possibly the most important observation from our study was the negligible toxic effects of streptomycin observed on our regime as compared with those reported by others using larger dosages and more frequent administration. Much of the early work on the use of streptomycin and its toxicity was done by the Mayo Clinic group. Hinshaw and Feldman,<sup>15</sup> Brown and Hinshaw,<sup>3</sup> Hinshaw, Feldman and Pfuetze<sup>17</sup> reported toxic effects from larger dosages (2-3 gm. per day) given for periods of

weeks to months. Important effects were: change to a positive Romberg test (broad base with eyes closed or ataxia on trying to walk a straight line); low-pitched tinnitus; prolongation of the caloric response; no true vertigo; only one case of spontaneous nystagmus; some degree of hearing loss in five cases. However, four of the five were cases of tuberculous meningitis. They also treated a few patients with a dosage of 1 gm. per day and found, "the dose of one gram per day is distinctly less toxic."

Fowler, Jr. and Seligman,<sup>13</sup> and Glorig and Fowler, Jr.<sup>14</sup> reported otic complications and labyrinthine functional upsets in patients receiving 1.8 - 2.0 gm. per day and others receiving 3.0 gm. per day of streptomycin. They list the following: vertigo, fine spontaneous nystagmus on lateral gaze, lessened caloric response (Kobrak), high tone loss recorded on the posttreatment audiogram in 65 per cent of cases, and change to broad-based gait in walking.

Wood<sup>26</sup> states that, administered over a long period, streptomycin frequently causes vertigo, nausea, and sometimes severe vomiting.

McDermott<sup>22</sup> puts greatest emphasis on the neurological reactions, but lists also a histamine-like reaction and irritation at the injection site due to impurities in earlier lots of the drug. He classifies the anaphylactic manifestations, such as fever, dermatitis without fever, eosinophilia without eruption, as not serious and as no indication to discontinue the use of streptomycin. Renal complications he attributes to kidney disturbances already present in the particular patient in question. Under the neurological reactions he discussed in detail vestibular dysfunction and deafness. Appearance of vestibular dysfunction varies with dosage: on one to two grams per day, about the fourth week; on three grams per day, the third week; with larger dosages, the second week. He described a "sensation like vertigo," nausea and vomiting, inability to walk, even in daytime, for six or eight months following treatment, and hypofunction of the vestibular apparatus. He records seven of 100 patients who had bilateral nerve deafness of 50 to 100 per cent after treatment. However, five of the seven had tuberculous meningitis, a fact which confuses the picture. Deafness was found in three types of cases: those in which an unusually high dosage of streptomycin was given, those in which there was renal insufficiency, and those in which the drug was administered intrathecally.

A more recent report on toxicity of streptomycin, from the Army, Navy and Veterans' Administration,<sup>1</sup> concerns 233 patients

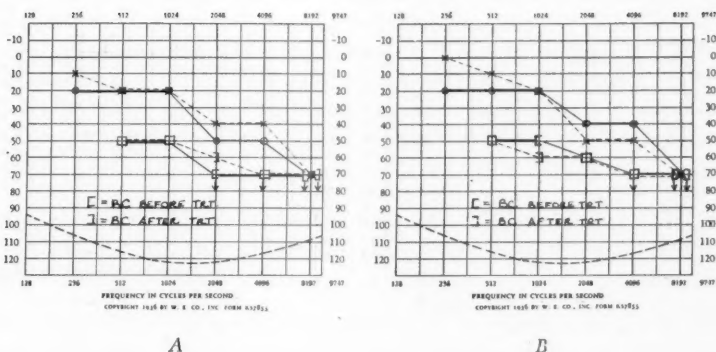


Fig. 9.—Audiograms made September 26, 1947, and December 27, 1947, of a patient, aged 72, with perceptive type of hearing loss, showing no change after treatment with streptomycin; A right ear; B left ear. o=before treatment; x=after treatment.

who have been followed on a daily dose of 1.8 gm. per day for 120 days. In this series some degree of vertigo accompanied by ataxia appeared in 92 per cent of cases. Onset of symptoms varied greatly as to treatment days. Diminution or absence of caloric response was found in 77 per cent of patients tested (111 of 144). Tinnitus occurred in approximately one half the patients. Audiometric readings showed "loss of hearing, sometimes in the low and sometimes in the high range, in five cases (2 per cent)." These changes were temporary except in one case in which they persisted. They believe that, unlike the vestibular disturbances, the deafness reversed itself not later than one month following treatment.

Briefly then, review of current literature on toxicity indicates that the following are common manifestations: vertigo, nystagmus, tinnitus (low-pitched), nausea, vomiting, positive Romberg test, ataxia on walking, and varying degrees and types of deafness, usually reversible except in cases of tuberculous meningitis. The vestibular changes frequently diminish in severity on withdrawal of the drug and any permanent damage is compensated for by the other senses after a time.

In our 12 cases toxic manifestations of any sort were notably few. In no patient was there a change found in the Romberg test, Kobrak caloric test, or audiogram. There was no nausea or vomiting. Two patients complained of slight dizziness about the eighth

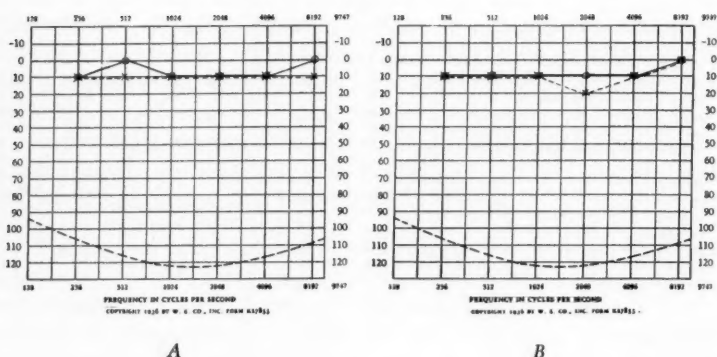


Fig. 10.—Audiograms made December 2, 1947, and March 7, 1948, of a patient, aged 19, with normal hearing, showing no change after treatment with streptomycin; A right ear, B left ear. o=before treatment; x=after treatment.

week. This was of a transitory nature and disappeared in a few days. It was not severe enough to interfere with appetite or to cause ataxia.

Whether or not the initial audiogram showed hearing loss, the streptomycin in one gram daily dosage seemed to have no effect on the hearing. The accompanying figures (Figs. 5 and 6) show the pretreatment and posttreatment audiograms of two patients. One (Fig. 5) was of a man, aged 72 years, showing nerve deafness (presbycusis and arteriosclerosis?). His curve was unchanged, as was also the other curve (Fig. 6), that of a woman, aged 19 years, with normal hearing.

It would seem justifiable to state that on the smaller one gram daily dosage of streptomycin, administered in two intramuscular injections, the toxic manifestations are inconsequential. None of the usual clinical tests or criteria for hearing loss and vestibular function changed from negative to positive. In fact they reflected no change.

#### DISCUSSION

A one gram daily dose of streptomycin divided into two intramuscular injections given at 12-hour intervals, without additional amounts of the drug being given locally by nebulization, results in

notably few toxic effects in treatment of laryngeal tuberculosis. In no case was there a change in the Romberg test, Kobrak caloric test, or audiogram. Yet the therapeutic results on this regime of smaller dosage are encouraging, being marked improvement in 12 cases and clinical cure in 10 of the 12. Supplementary thiamine hydrochloride in six cases caused no detectable difference in healing rate.

Of importance is the early loss of odynophagia in streptomycin-treated patients. This improves the general prognosis by allowing better dietary measures.

The following advantages could also be listed: (1) The patient is disturbed only twice in 24 hours (6:00 a. m. and 6:00 p. m.) for injections, so his all-important rest is not interfered with. (2) The patient is spared the expense of oxygen and special equipment and additional disturbance for frequent local nebulization treatment. (3) One gram of streptomycin is only half the expense of two grams. (4) Absence of toxic manifestations, nausea and vomiting, allows an uninterrupted dietary management.

#### SUMMARY

1. Twelve cases of tuberculous laryngitis in patients with advanced pulmonary disease were treated with streptomycin. An audiogram, Kobrak caloric test and Romberg test were run at the beginning and end of therapy.

2. A daily dosage of 0.8 to 2.0 gm. administered every four hours for 90 to 120 days has been advocated. We used one gram per day divided into two doses given at 12-hour intervals for 90 days.

3. Whereas results from aerosol treatment alone have been discouraging, this method combined with intramuscular administration has been successful. In addition, reports in the literature indicate promising results with intramuscular use only. The latter technique was employed in our cases.

4. Occurrence of tuberculous laryngitis makes the prognosis in a case of pulmonary tuberculosis more grave. Treatment with streptomycin has resulted in cures of the larynx. In our group all patients improved. Ten of the 12 were cured of laryngeal tuberculosis. Thiamine hydrochloride given simultaneously by mouth in six cases did not accelerate healing.

5. Toxic effects generally listed are: positive Romberg test with ataxia, low-pitched tinnitus, prolonged caloric response, vertigo, nausea, vomiting and hearing loss. In our cases no patient had a change in the audiogram, Kobrak caloric test or Romberg test. Two patients had slight transitory dizziness about the eighth week, lasting a few days, not severe enough to interfere with meals.

The author wishes to express appreciation to the Western Electric Company for permission to reproduce in part the copyrighted audiogram chart "Form KS-7855 WECO"; to Dr. Claude C. Cody, Professor of Otolaryngology, Baylor Medical College, Houston, for his counsel on this project; and finally to his wife, Denise Withers, for the drawings.

7438 HARRISBURG BLVD.

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# The Scientific Papers of the American Broncho-Esophagological Association

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LXV

## THE USE OF STREPTOMYCIN IN TUBERCULOUS TRACHEOBRONCHITIS.

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The advent of streptomycin and its addition to our therapeutic regimen have changed the concepts of management of tuberculous bronchitis from those of empiricism to those of intelligent rationale. Results of experimentation and clinical investigation defining its suppressive action on the course of certain types of pulmonary tuberculosis are remarkable.

Tuberculous tracheobronchitis has long been a problem of disagreeable consequence. With its associated edema, ulcerations, granulations, and stenoses, acting as obstructive phenomena, it has prolonged the course of the disease, interfered with proper execution of collapse therapy, and been the cause of such complications as atelectasis and bronchiectasis. Therapy, although having run the gamut of the pharmacopeia, has been totally inadequate—if not useless. This paper represents the results obtained in the treatment of such patients with streptomycin at the Barton Memorial Division of the Jefferson Hospital.

Feldman and Hinshaw,<sup>1</sup> in September 1945, published the first report concerning the use of streptomycin in man. In a preliminary paper dealing with pulmonary tuberculosis of various forms, these authors remarked on the improvement, which was so rapid as to be in no other wise explainable than through the merit of streptomycin. The following year, Figi and Hinshaw<sup>2</sup> reported four cases

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of tuberculous laryngitis treated with streptomycin, all of which showed either complete healing or satisfactory clinical regression within an unprecedented six weeks' time. Recently, in November 1947, Brewer and Bogen<sup>3</sup> published their results in the use of streptomycin in 44 cases of tuberculous tracheobronchitis. Their summary emphasizes the necessity for adequate dosage and presents the advantages of various methods of administration.

Results such as these in the treatment of any disease entity are most encouraging, and particularly so in tuberculous tracheobronchitis and laryngitis, wherein all prior forms of therapy have been so fruitless.

In spite of such promising results, the limitations in the use of streptomycin are manifest and real. The most frequently encountered are those grouped under the heading of "toxic reactions." Of these, the most serious is a histamine-like reaction, probably due to protein impurities and rather uncommon in the more recent issues of the drug. Sensitization symptoms are not infrequent, nor are those of renal failure in patients with known renal dysfunction. Involvement of the cochlea and labyrinth have been the most distressing toxic manifestations heretofore; modifications in total daily dosage have lessened their incidence. Of equal consequence, but less well appreciated, is the development of streptomycin-resistant strains, occurring in instances of prolonged administration. Recent reports indicate that this, rather than being an acquired trait, is the "survival and multiplication of a small number of inherently resistant organisms."<sup>4</sup>

In the selection of patients for our study, two criteria were used: bronchoscopic evidence of mucosal disease as manifested by persistent ulcerations, granulations, and stenoses; roentgen signs of obstructive phenomena as seen in atelectasis or in the ballooning of cavities following collapse measures. All patients were proven tuberculous.

There was no interference or disruption of the routine of sanatorium care. On patients recently admitted, no new forms of collapse therapy were initiated until satisfactory repair of the mucosal disease had been accomplished. Those already having had effective collapse measures were kept on them. Those initially evidencing obstructive roentgen signs were managed in the accepted manner, streptomycin being added as an adjunct of questionable merit. The cases were then divided into groups according to the method of administration of streptomycin.

Accordingly, a total of 62 patients were selected for study. Of these, 44 satisfied the bronchoscopic requirements, 18 additional evi-

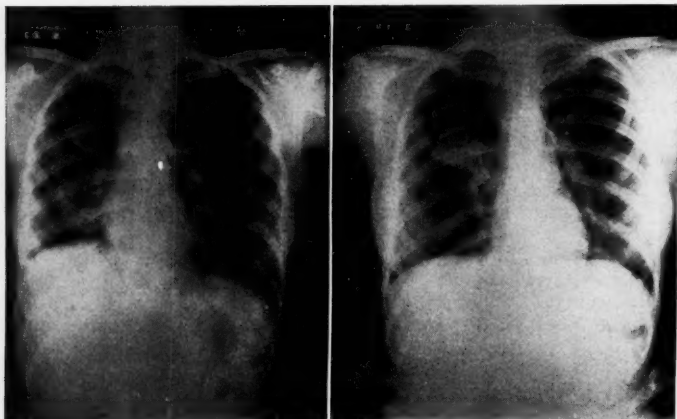


Fig. 1.—*a*, Roentgenogram made at two months' interval, showing the development of atelectasis of the right upper lobe. *b*, Although pneumothorax therapy was abandoned, the atelectatic lobe failed to re-expand.

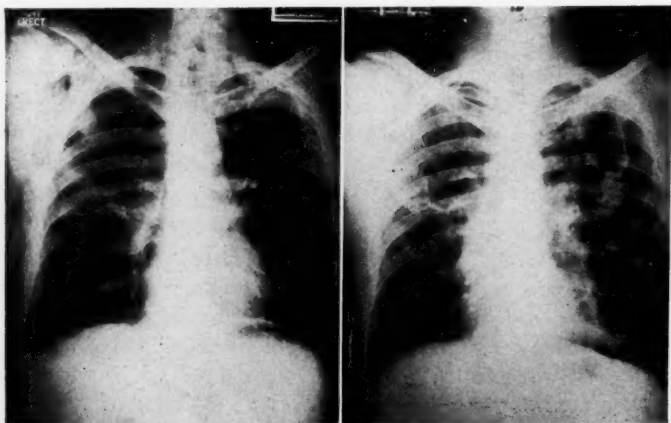


Fig. 2.—*a*, Roentgenogram of a giant cavity of the left upper lobe. *b*, Roentgenogram illustrating failure of cavity collapse by induced pneumothorax therapy; "bollooning" of cavity by check-valve bronchial obstruction.

TABLE 1.—SIGNS OBSERVED IN TUBERCULOUS TRACHEOBRONCHITIS.

	No.	%
BRONCHOSCOPIC: 44 patients		
Localized Ulcerations	9	20.4
Diffuse Ulcerations	23	52.2
Inflammatory Stenosis	12	27.2
ROENTGENOGRAPHIC: 18 patients		
Atelectasis	4	22.2
Ballooned Cavities	14	77.7

dencing roentgen signs of bronchial obstruction. Eleven patients received streptomycin by aerosol alone, 15 by concomitant aerosol and parenteral administration, and 36 by parenteral administration alone. The aerosol solution consisted of 50 mg. of the drug in 1 cc. of sterile isotonic sodium chloride solution, administered by nebulization every two hours, for a total daily dosage of 500 mg. Parenteral administration consisted of the intramuscular injection of 500 mg. twice daily. Larger parenteral dosages had been used originally, but because of untoward reactions, the total daily dosages have been modified.

The incidence of the signs observed, both bronchoscopic and roentgenographic, are represented in Table 1. It is apparent that several cases manifested multiple signs; it is likewise apparent that various roentgenographic manifestations of obstruction lack bronchoscopic corroboration. This is not particularly significant when one is mindful of the fact that many of the bronchial subdivisions are bronchoscopically inaccessible to direct view. Of signal importance are the following facts: that all cases selected bronchoscopically exhibited evidences of severe and long-standing activity; that all cases selected roentgenographically had failed to respond to conventional forms of management.

#### RESULTS

The results generally have been forcefully impressive. In those cases uncomplicated by obstructive effects, regression and repair of the bronchial lesions have progressed often with dramatic rapidity. Reexaminations, at intervals of four and six weeks' time, frequently have shown complete healing of mucosal ulcerations and dissolu-

TABLE 2.—RESULTS OF STREPTOMYCIN THERAPY IN TUBERCULOUS TRACHEOBRONCHITIS.

PATIENTS SELECTED BRONCHOSCOPICALLY.

	CONCOMITANT PARENTERAL AND AEROSOL	PARENTERAL ALONE		AEROSOL ALONE
		2 GM./DAY	1 GM./DAY	
Healed	9	4	5	1
Improved	1	2	9	6
Unimproved	0	0	4	3

tion of granulations, without the consequent development of cicatricial stenoses.

The results thus enumerated in Table 2 emphasize primarily the necessity for adequate streptomycin dosage; both the parenteral administration method, using 1 gm. per day, and the aerosol method give insufficient dosages, though they are not ineffective. Moreover, though larger doses administered parenterally are effective, they are prone to produce untoward effects. The concomitant parenteral-aerosol method of administration, using the smaller absorbable dosage, appears to be the method of choice.

The results obtained in those cases initially presenting roentgen evidences of bronchial obstruction are shown in Table 3. Previously, although appreciated as being due to endobronchial mucosal disease, such complications rarely responded to any form of therapy. Study of this table shows that sufficient regression of the obstructing bronchial lesions was obtained to allow for reexpansion in all instances of atelectasis and for eventual effective collapse in the cases of giant cavities; that, too, to be effective in such instances streptomycin must be administered in relatively large dosages.

## SUMMARY

A clinical study of the use of streptomycin in tuberculous tracheobronchitis shows it to be a drug of significant importance. Healing of mucosal ulcerations and resolution of obstructive phenomena have been effected in a large percentage of instances. The concomitant parenteral-aerosol method of administration of streptomycin appears to be the method of choice.

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TABLE 3.—RESULTS OF STREPTOMYCIN THERAPY IN TUBERCULOUS TRACHEOBRONCHITIS.

PATIENTS SELECTED ROENTGENOGRAPHICALLY.

CASE NO.	ROENTGEN FINDINGS		ENDOSCOPY FINDINGS		STREPTOMYCIN ADMINISTRATION			RESULTS				
	ATELECTASIS	BALLOONING OF CAVITIES	STENOSIS	ULCERATIONS	NORMAL	PARENTERAL	COMBINED	AEROSOL	ATELECTASIS REEXPANSION	CAVITY COLLAPSE	HEALING OF ULCERATIONS	GRANULATIONS DISSOLVED
1	*		*			*			*			*
2	*				*	*			*			
3	*		*				*		*		*	*
4	*		*				*		*			*
5		*		*		*				*	*	
6		*	*	*		*				-†	*	*
7		*		*			*			*	*	
8		*	*	*				*		-	*-	*-
9		*			*	*				*		
10		*			*	*				*		
11		*	*	*		*				*	*	*
12		*	*	*		*				*	*	*
13		*		*		*				*	*	
14		*	*	*			*			*	*	*
15		*	*	*			*			*	*	*
16		*		*		*				*	*	
17		*	*			*				*		*
18		*	*			*				*		

†Cavernostomy for drainage.

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BRONCHOSCOPIC OBSERVATIONS ON THE PULMONARY  
ASPECTS OF FIBROCYSTIC DISEASE OF THE  
PANCREAS

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The bronchologist is frequently consulted to give aid in treating the chronic pulmonary infections of childhood. The solution of local problems, such as bronchial obstruction by foreign body or inspissated mucus, are often of basic importance and may be achieved by bronchologic methods. However, all realize that the general physiologic state of the patient is one of the most significant elements controlling the course of any infection. The abnormal response of the diabetic to infection and the power of artificially stimulated antibodies to protect against diphtheria are examples of the profound effect of systemic influences in infection.

A combination of local and systemic factors may be recognized in bronchopulmonary infections of the allergic patient. Here the fundamental systemic defect of altered reactivity to the allergen may be reflected in the lung acting as the shock organ to produce bronchial asthma. A similar close relationship to the systemic disturbance must be recognized in the chronic pulmonary infection associated with fibrocystic disease of the pancreas. Landsteiner<sup>1</sup> in 1905 made the first accurate observations of this entity. A recent thorough review and evaluation of the literature has been made by Anderson.<sup>2, 3</sup>

The disease is believed to be congenital and familial. There is cumulative evidence that the disease may appear in several branches of the family tree. This body of data provides support for the hypothesis that "cystic fibrosis of the pancreas is the expression of a hereditary factor."<sup>3</sup> The disease is characterized by an absence or diminution of pancreatic enzymes with poor utilization of protein, starch, fat and fat soluble vitamins. Clinically, this disease develops early in infancy, the patients show a failure to gain on normal diet, have an excellent appetite, produce large foul stools and are

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prone to develop repeated upper respiratory infections, chronic bronchitis, bronchopneumonia and bronchiectasis.

It was found to be present in about 3 per cent of the necropsies at Babies' Hospital, New York City.

The fundamental pathological condition in cystic disease of the pancreas has been adequately demonstrated by Landsteiner,<sup>1</sup> Passini,<sup>4</sup> Anderson,<sup>2,3</sup> Farber<sup>5</sup> and Glanzman,<sup>6</sup> but the interrelation of the process among the various organs described and the sequence of the pathological spread is still debatable.

Farber<sup>5</sup> was able to show, by postmortem examination of 87 infants and children with pancreatic insufficiency, that the "finding of inspissated materials in the mucus glands of the trachea, bronchi, esophagus, duodenum, gall bladder, salivary glands and even in accessory pancreatic tissue gives evidence that the pancreas is only one of many structures of the body involved in a process, the basic feature of which is the physical alteration of secretion, which inspissates, obstructs and causes dilatation of acini or mucus structures in various parts of the body." He states that "an explanation for the pertussis-like respiratory complaints may be found in the thick mucus which is produced in the trachea and bronchi and which is expelled with difficulty. The accumulation of thick mucus causes respiratory obstruction. The failure of lubrication of ciliated epithelium in the respiratory tract due to the lack of normal thin mucus permits secondary infection with staphylococcus aureus of relatively low virulence. The respiratory signs therefore depend on primary obstruction by thick mucus, failure of proper lubrication of ciliated epithelium and secondary staphylococcal infection." The pathogenesis of the various anatomic changes points uniformly to a disturbance in the enterobronchial canal systems caused by abnormal viscosity of the secretions. Farber suggests that "the physical character of the mucus produced indicates the possible importance of either a deficiency or an insufficiency of the mucinase required for the maintenance of mucus in a normal physical state." Glanzman's<sup>6</sup> investigations have led him to a similar conclusion concerning the pathogenesis of this disease.

A somewhat contradictory opinion has been given by Anderson,<sup>2</sup> who states that "the bronchial glands appear (anatomically) normal in most cases; the pulmonary infection is secondary to the nutritional difficulty resulting from lack of pancreatic function; vitamin A deficiency contributes to it, but other factors should be searched for." She favors the view that the pulmonary lesion be-

gins after birth and is primarily the result of nutritional deficiency. On the basis of the clinical picture Anderson divides these patients into three groups: 1) those with congenital intestinal obstruction, 2) those with early appearance of symptoms and death before the sixth month, 3) those who survive longer and present the celiac syndrome complicated by respiratory infection.

The patients whom we have seen fall into three clinical patterns: those whose predominating symptoms are gastro-intestinal and nutritional and who are usually recognized as having fibrocystic disease; those in whom the respiratory symptoms dominate the picture, the group most likely to be seen by the bronchologist; and those in whom both respiratory and gastro-intestinal symptoms are evident.

The roentgen examination of the chest of these children frequently fails to demonstrate changes commensurate with the degree of functional disturbance. The roentgenograms of several of these children have been reported negative. More commonly, increased hilar density with exaggeration of hilar markings are seen. With these may be associated mottling of the lung fields, localized infiltrations, widening of the mediastinal shadow, or emphysema. Differential diagnoses suggested by the roentgen examination include tuberculosis, bronchiectasis, bronchopneumonia, atypical pneumonia, asthma, fungus infection and whooping cough.

Bronchoscopic examination of these children presents fairly characteristic findings. The tendency of the pulmonary infection to subside and flare up produces a variation in the intensity of the picture but this usually is not sufficient to be confusing. A few of these may present the picture of tracheobronchitis with the usual moderately thin mucopurulent secretion. The common picture is that of a hyperemic sometimes granular mucosa with thickening of the bronchial spurs. On introduction of the bronchoscope the lumen is obscured by the presence of extremely viscid, purulent or, occasionally, blood-stained mucus. When this is aspirated the hyperemic bronchus shows marked expiratory intrusion of the posterior bronchial wall into the lumen producing a bronchus whose cross section is crescentic. In this respect the bronchus resembles that seen in the asthmatic patient. The marked reduction of pulmonary reserve is manifested by the frequency and severity of the cyanosis which occurs during bronchoscopy. The routine use of oxygen insufflation through the bronchoscope during the examination greatly reduces the frequency of cyanosis but does not always prevent it. Indeed, these children often become cyanotic during the paroxysms

of pertussis-like cough which are such a prominent feature of the respiratory symptoms.

Bronchoscopic aspiration usually relieves the obstructive character of the respiration and causes symptomatic improvement. The duration of this improvement is variable, sometimes being less than 24 hours. Repeated bronchoscopic aspiration may reduce the viscosity of the secretion. The bronchopulmonary drainage being thus improved, antibiotic and chemotherapeutic drugs are more effective.

Of the organisms present in the bronchial secretion *Staphylococcus aureus* was found in all but one patient. This patient showed *Bacillus pyocyaneus* in pure culture. Other organisms found were *Streptococcus viridans*, *pneumococcus*, diphtheroids, *Micrococcus catarrhalis*, hemolytic streptococci, *Escherichia coli* and *Haemophilus influenzae*.

The following cases are typical examples of the problem as it concerns the bronchologist.

#### REPORT OF CASES

CASE 1.—This patient, E. A. B., a white male, was admitted at the age of three months with the chief complaint of cough, dyspnea and cyanosis. The cough had begun at the age of two weeks and had persisted from that time. Before admission a diagnosis of left lower lobe pneumonia had been made. The child had failed to improve on antibiotic and pancreatin therapy.

On admission he appeared well developed but was coughing and cyanotic. There was retraction of the chest wall and fine dry râles were heard over the right lung. The roentgenogram of the chest (Fig. 1) showed a severe bronchopneumonia. Although there was no clinical improvement, there was some clearing in the roentgen film of the chest taken on the eighth hospital day. A repeat examination on the eighteenth day showed bilateral emphysema, infiltration in the left base, and a triangular density of the right base.

Increasing dyspnea and respiratory obstruction became more marked. Bronchoscopic examination done on the twenty-second day disclosed the typical bronchoscopic picture described previously. The child appeared more comfortable after bronchoscopic aspiration but on the following day the obstructive secretion again accumulated and he died in respiratory failure.

The diagnosis of fibrocystic disease which had been made clinically was completely supported by the necropsy findings.

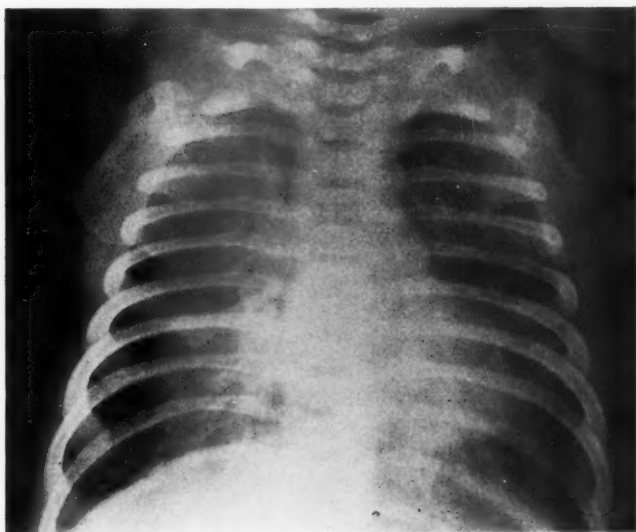


Fig. 1, Case 1.—Roentgenogram of the chest made on the eighteenth day after admission. It shows bilateral emphysema, infiltration in the left base and a triangular density of the right base. Bronchoscopic examination was done on this patient four days later.

CASE 2.—This white female, F. S., was admitted when five months old. She was well until two months before admission when she developed pneumonia. Following this illness she had a persistent cough which was her chief complaint on admission. Just prior to admission her breathing had been "heavy" and noisy. The family physician had recognized an unexplained roentgen shadow in the right upper lobe of her chest. She was admitted for investigation of this shadow.

Physical examination revealed malnutrition, inspiratory retraction of the lower rib margins, and occasional râles in the right hilar region.

Roentgen examination of the chest (Fig. 2) confirmed the finding of a circumscribed mass in the upper half of the right mediastinal region.

Bronchoscopic examination disclosed bilateral bronchial hyperemia with expiratory intrusion of the posterior bronchial wall. A

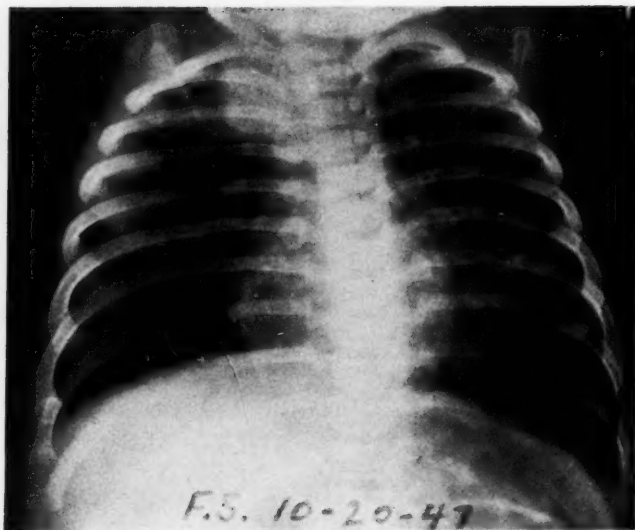


Fig. 2, Case 2.—Roentgenogram showing a shadow in the right upper lobe area for which the patient was admitted. The diagnosis of fibrocystic disease of the pancreas was suspected when bronchoscopic findings were found to be incompatible with other clinical evidence.

large quantity of purulent, moderately viscid secretion was present, chiefly in the left lung.

The incompatibility of the clinical and the bronchoscopic findings suggested a further search into the etiologic factors in this patient's disease. We then found that during her hospital stay she had failed to gain weight despite an adequate caloric intake. Studies of her duodenal secretions were then made. Trypsin was entirely absent and amylase and lipase were present in abnormally low concentration. The fat content of the stools was increased.

The recognition of the fibrocystic disease as the cause of her pulmonary symptoms probably saved this child from exploratory thoracotomy and permitted her to be discharged with an appropriate plan of treatment.

CASE 3.—K. C., a 3½-year-old boy, who had been subject to frequent respiratory infections and wheezing since the age of six months, developed transient paroxysms of cough five months

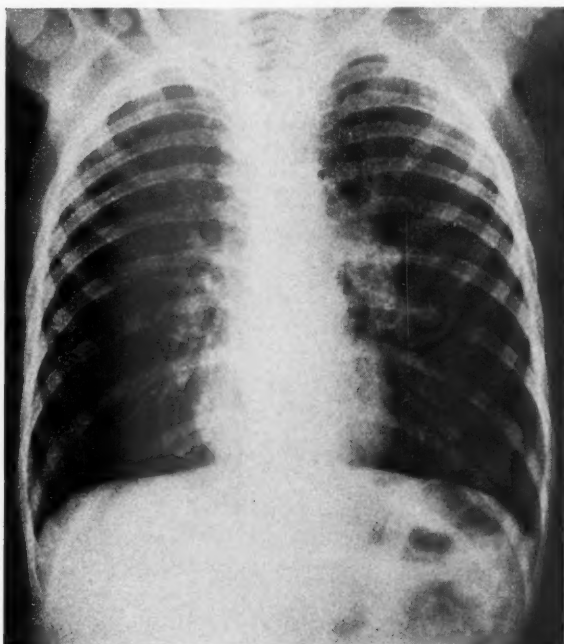


Fig. 3, Case 3.—Roentgenogram taken at the time of the first admission. It shows the severe emphysema associated with the obstruction of the tracheobronchial tree by viscid mucus.

before admission. Two months before admission he had a severe chest cold with physical findings suggestive of bronchopneumonia and pertussis. Cough plates for *Haemophilus pertussis* were negative. He did not recover completely from this illness. One month before admission his cough became productive and the respiratory distress more severe.

On admission he appeared moribund. Physical examination disclosed extreme cyanosis and dyspnea, an emphysematous chest with deep suprasternal and episternal retractions, coarse breath sounds with fine moist râles throughout both lungs, fever, abdominal distention and the early signs of cardiac failure.

Roentgen examination of the chest showed bilateral emphysema and some cardiac enlargement (Fig. 3).



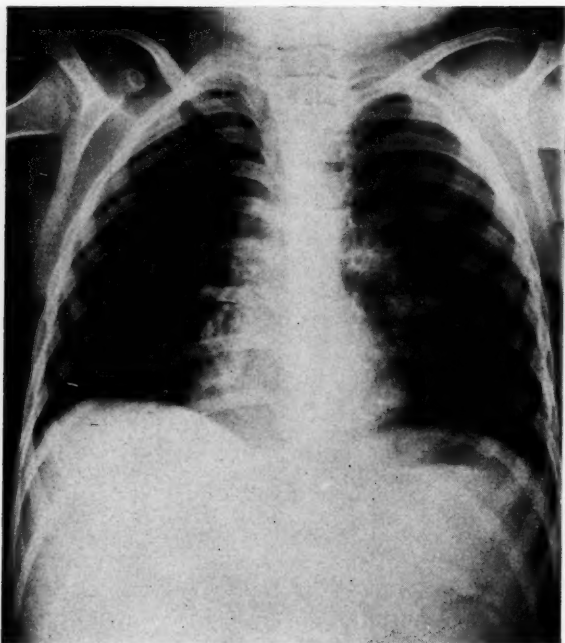


Fig. 4, Case 3.—Roentgenogram made at the time of discharge after the first admission. The emphysema has disappeared and the lungs are clear to physical examination.

Bronchoscopic examination was done one hour after admission. The tracheobronchial tree was filled with thick, viscid secretion which accumulated in the specimen collector in gummy chunks which would not coalesce. This secretion was acting as a foreign body to produce serious obstruction to the airway. The tracheobronchial tree presented the appearance described above.

Following bronchoscopy there was definite but partial improvement in the child's condition. Oxygen therapy, digitoxin and penicillin were given. Bronchoscopic aspiration was repeated twice weekly. With this therapy his condition improved and the fever subsided on the third day.

The diagnosis of fibrocystic disease was confirmed by the finding of abnormally large amounts of fat in the feces and the absence of trypsin in the duodenal secretions.



Fig. 5, Case 3.—Roentgenogram made after recurrence of symptoms following tonsillectomy, showing diffuse mottling of the lung fields.

When *H. influenzae* appeared in the cultures of the bronchial secretions, which originally contained hemolytic staphylococcus aureus and hemolytic streptococci, aerosol streptomycin was given.

After six weeks the bronchial secretions had diminished in amount. The extreme viscosity was no longer present but the secretions were still definitely viscid. At this time hyaluronidase was found to produce better dispersion of this child's secretion in vitro than water or sodium chloride solution. The aerosol streptomycin was discontinued and aerosol hyaluronidase was given. Following this change in therapy the bronchial secretions became more fluid and trypsin was found in the duodenal secretions. The concentration of trypsin, lipase, and amylase were still abnormally low.

By the twelfth week bronchoscopic aspiration was discontinued as it was no longer necessary. Physical examination of the heart

and lungs was negative but he retained the dour expression and the protuberant abdomen so commonly seen in this disease (Fig. 4).

Following his discharge he did well for six months but he returned to the hospital in a similar, but less acute, condition following a relapse apparently resulting from tonsillectomy (Fig. 5). At the time of this writing he is improved but still under treatment. A detailed report of this case will be made at a later date.<sup>7</sup>

The prognosis for life in these children is poor. The earlier in life they develop symptoms requiring hospital admission the worse the prognosis. The bronchologist may contribute to the relief of the pulmonary symptoms and, in some cases, to the prolongation of life. He should also bear in mind the possibility of encountering this disease when confronted with the problem of chronic respiratory infection in childhood.

#### SUMMARY

1. Fibrocystic disease of the pancreas is characterized by an absence or diminution of pancreatic enzymes, poor utilization of protein, starch, fat and fat soluble vitamins, and the passage of large, foul, fatty stools. It develops in early childhood. The patients fail to gain weight despite an excellent appetite and are prone to develop respiratory infection which may represent an integral part of the disease.

2. The respiratory symptoms sometimes dominate the clinical picture and resemble chronic respiratory infection due to other causes.

3. Bronchoscopic examination will reveal pathologic changes which are sufficiently definite to suggest the diagnosis.

4. Bronchoscopic aspiration gives symptomatic relief and may aid in prolonging life.

5. Fibrocystic disease of the pancreas must be considered in the differential diagnosis of the chronic pulmonary infections of childhood.

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LXVII

BRONCHOSCOPY IN THE NEWBORN: AN ANALYSIS OF  
FIFTY CASES

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(by invitation)

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The possibility of applying bronchoscopy to the solution of some of the problems involving respiratory disturbances in the newborn has received relatively little attention. The obstetrician and the pediatrician, largely as the result of the efforts of Flagg, Henderson and others, are fully aware of the value of catheter-suction cleansing of the upper air passages and the trachea as well as the stimulating effects on the respiratory center of the insufflation of oxygen mixed with small amounts of carbon dioxide. The lives of countless newborn infants have been saved by the prompt application of these established methods. Many bronchoscopists, however, feel that additional lives may be saved and subsequent respiratory complications of the neonatal period reduced by the wider use of the bronchoscope in selected cases when the patient fails to respond promptly to these recognized procedures.

Unfortunately, although improved instruments for this work have been designed by Jackson, Tucker, Jesberg and Holinger, few reports of actual experiences in this field have been recorded. In 1942 Woodward and Waddell<sup>1</sup> reported bronchoscopy in five cases of atelectasis in newborn infants and cited the experiences of Buckles in 17 additional patients. House and Owens<sup>2</sup> in 1946 reported a series of 23 newborn infants on whom bronchoscopies were done because of congenital atelectasis. Both of these authors agree that bronchoscopy can be performed with safety even in the prematurely born infant and that it should be more widely employed in cases of persisting obstruction and atelectasis. It is obvious that if bronchoscopy is to be extended to this field, every effort must be made

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not only to establish its safety but also to clarify the indications for its usefulness. It is equally evident that these ends can be accomplished only by accumulated reports of experiences in this field as well as by the general discussion which presentations such as this may invite.

In approaching the subject of the bronchoscopic treatment of respiratory problems of the newborn, it is important to review certain observations pertaining to the physiology of neonatal respiration. At birth the lungs are collapsed and relatively solid. When air is introduced by normal respiratory movements, the alveoli gradually expand but several days may elapse before air is uniformly distributed throughout all the alveoli. The anterior portions of the lungs are the first to be inflated, then the upper lobes and finally the lower lobes posteriorly. It is important to emphasize that the tissues about the hilus and posterior portions of the lobes are normally the last areas to aerate in spite of the fact that diaphragmatic breathing predominates during the first few days of life. The studies of Farber and Wilson<sup>3</sup> indicate that at least two to four days are normally required for complete expansion of all portions of both lungs in the full term, normally breathing infant and that a period up to six weeks or longer may be required to inflate fully the lungs of a premature infant. Atelectasis, therefore, in the immediate neonatal period should properly be considered to be of clinical importance only when it is extensive and persistent enough to be symptom-bearing.

It has been conclusively demonstrated in experimental animals by Barcroft and Barron<sup>4</sup> as well as by Rosenfeld and Snyder<sup>5</sup> that intra-uterine respiratory movements normally occur and that the development of the alveoli is dependent not only upon these fetal respiratory excursions but also upon the to-and-fro flow of amniotic fluid within the respiratory passages. In the human fetus, however, the existence of intra-uterine respiratory movements as well as the free passage of amniotic fluid within the air passages is still somewhat controversial. Potter and Adair<sup>6</sup> have reported the autopsies of two cases which seem to disprove the contention that the free passage of amniotic fluid is essential for normal alveolar development. It is of clinical importance, nevertheless, to emphasize that regardless of this point amniotic fluid is regularly present in the upper air passages as well as in the trachea and large bronchi of the newborn and with the first deep breath taken after delivery is in varying amounts drawn into the deeper portions. Breech presentation, version, and cesarean section, in which the full compressing

effects of the perineum are lacking, tend to leave the respiratory tract filled with fluid which must be removed by artificial means. The lungs of infants dying of pneumonia directly after birth frequently show on section bronchioles and alveoli filled with amniotic fluid and epithelial cells. Actual massive aspiration is usually considered to be exceptional, but according to Holt and McIntosh<sup>7</sup> is more frequent than is generally supposed. Farber and Wilson reported this finding in 15 per cent of a series of 100 full term infants dying when less than two days of age. It is further pointed out by Holt and McIntosh that the respiratory difficulty caused by aspirated secretions may not be immediate and obvious but that somewhat later the secretions may become thickened and membrane-like, resulting in conspicuous respiratory obstruction which frequently ends in pneumothorax from ruptured alveoli and death.

The respiratory disturbances in the newborn may be considered as three distinct, although frequently associated, clinical entities: primary respiratory failure, respiratory obstruction and persistent atelectasis. The term asphyxia neonatorum includes a great variety of conditions which give rise to deficient oxygenation of the blood. Potter and Adair<sup>6</sup> list the conditions interfering with the establishment of normal respiration as follows:

CONDITIONS INTERFERING WITH THE ESTABLISHMENT  
OF NORMAL RESPIRATION

- A. Abnormalities of the central nervous system:
  - (1) Malformations of the brain
  - (2) Depression of the respiratory center by
    - a) Pressure from intracranial hemorrhage
    - b) Cellular injury from anoxemia
    - c) Cellular injury from drugs
  - (3) Immaturity of the cells of the respiratory center
- B. Abnormalities of the lungs
  - (1) Immaturity of the parenchyma with insufficient alveolar development to permit gaseous exchange
  - (2) Hypoplasia of lung tissue caused by deficit of germ plasm
  - (3) Obstruction of bronchi and alveoli
    - a) Aspiration of amniotic fluid, meconium, blood, mucus
    - b) Intrauterine pneumonia
- C. Mechanical Compression of lungs
  - (1) Subdiaphragmatic pressure
    - a) Polycystic kidneys
    - b) Intestinal distension
    - c) Peritoneal effusion, etc.
  - (2) Intrapleural Pressure
    - a) Diaphragmatic hernia
    - b) Massive cardiac hypertrophy
    - c) Pleural effusion, etc.



Farber and Wilson consider the causes of persistent atelectasis to be (1) an imperfectly developed or injured respiratory center, (2) an imperfectly developed thoracic mechanism and (3) bronchial obstruction due to aspiration of the contents of the amniotic sac, mucus or blood. The latter cause is considered by these authors to be of greater importance in full term than in premature infants. It is also of interest in this connection to note the opinion of Holt and McIntosh that the most frequent cause of pneumothorax in the newborn is incomplete bronchial obstruction from aspirated amniotic contents or, more rarely, mucous plugs. Atelectasis in the newborn, according to Coryllos,<sup>8</sup> is maintained by the same mechanism by which it is produced in later life, namely bronchial obstruction. The observations of Cruickshank, Wasson, Von Reuss<sup>9</sup> and many others have fully demonstrated that pneumonia consequent upon unrelieved atelectasis causes two-thirds of all deaths in the neonatal period. The importance of every procedure which will safely remove accumulated and retained bronchial secretions and hasten the establishment of normal aeration is apparent.

As the basis for this report a series of 50 bronchoscopies performed in newborn infants was reviewed. The indication in all instances was clinical evidence of respiratory distress persisting in spite of the usual methods of conservative treatment. It should be emphasized at once that the immediate resuscitation of the newborn is not properly the responsibility of the bronchoscopist and that all recognized measures must be carried out by the obstetrician at the time of birth. In cases, however, in which evidence of persistent or progressive respiratory obstruction occurs, the possibility of bronchoscopic aid should, in our opinion, be carefully considered. As Coryllos has emphasized, the most important measure in asphyxia and atelectasis of the newborn is to eliminate mechanical obstruction not only in the larynx but also in the tracheobronchial tree. Markedly diminished thoracic expansion, suprasternal retraction, continued or recurring cyanosis, suppression of breath sounds over a considerable area of one or both lungs, coarse, moist inspiratory râles, all suggest atelectasis secondary to bronchial obstruction.

The majority of the bronchoscopies performed in this series were done within the first 48 hours of life. In several instances the possibility of other conditions interfering with the establishment of normal respiration was fully recognized. It must be understood, however, that the clinical condition of many of these infants does not permit the careful differential studies necessary under more favorable circumstances.

In our experience bronchoscopy produces little, if any, shock in these infants. This coincides with the reports of other observers. The glottis is relaxed and with proper sized tubes no evidence of laryngeal edema develops. No tracheotomies were necessary in this series. Death occurred in 15 cases. Subsequent postmortem examination showed that the causes of death included cerebral hemorrhage (5 cases); congenital defects—vascular abnormalities, diaphragmatic hernia, massive atelectasis unassociated with bronchial obstruction (3 cases); pneumonia (2 cases); prematurity (5 cases). In no case was any evidence of laryngeal injury visible.

The analysis of the bronchoscopic findings in the 35 surviving newborn infants shows several points of distinct interest. In 20 cases varying amounts of obstructing secretions were aspirated from the bronchial tree. In six cases thick, stringy plugs of secretion were found blocking a main bronchus. In four cases practically no secretions or evidence of obstruction was encountered. In one case a web was discovered almost completely blocking the mouth of the left main bronchus and in another case a thin partial subglottic diaphragm was present. A complete paralysis of the left vocal cord was observed in one infant. One infant was bronchoscoped 48 hours after birth because of obstruction resulting from the aspiration of breast milk.

One of the most interesting cases in this series was of an infant presenting a tracheo-esophageal fistula. Successful surgical closure was carried out on the third day of life. An important part of the successful management of this case was the careful bronchoscopic aspiration of secretions both preliminary to and following operation. Bronchoscopy, we believe, will play an increasingly important part in the management of similar surgical problems in the newborn.

#### CONCLUSIONS

- (1) Experience in this as well as other reported series indicates that bronchoscopy can be performed with safety in the newborn.
- (2) Bronchoscopy in our opinion is indicated in selected cases of respiratory obstruction and atelectasis which fail to respond to conservative treatment.
- (3) In such cases it may not only prove to be life-saving but by removing obstructions in the tracheobronchial tree may reduce the complications from persistent atelectasis in the neonatal period.

(4) The usefulness of bronchoscopy in conjunction with certain surgical procedures in the newborn, notably the closure of tracheo-esophageal fistula, is illustrated by a recorded case.

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LXVIII

TRACHEAL AND BRONCHIAL OBSTRUCTION DUE TO  
CONGENITAL CARDIOVASCULAR ANOMALIES

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Recent achievements in thoracic surgery and advances in diagnostic techniques have aroused new interest in congenital cardiovascular anomalies. Certain of the major anomalies are now being routinely and successfully treated by surgery, and the utilization of surgical methods in this field is rapidly being broadened. If full advantage of these newer procedures is to be realized, it is imperative to recognize these developmental defects promptly and to differentiate the specific types amenable to surgery.

This paper is concerned primarily with a limited group of cardiovascular anomalies that produce respiratory dysfunction through compression of the trachea and bronchi. These causative factors of severe and often fatal constriction of the tracheobronchial tree, although well known anatomically for many years, have not been stressed clinically because of the lack of successful therapy. In view of the recent advances, these conditions now merit careful and thorough analysis. While they are relatively rare, they frequently present striking clinical pictures of pulmonary disease which often are explained only by the postmortem examination. As in most severe types of bronchial obstruction, whether produced by an intrabronchial, endobronchial, or extrabronchial lesion, that resulting from cardiovascular anomalies manifests itself chiefly by obstructive emphysema or atelectasis. The small caliber of the infant trachea and bronchi is responsible for the extensive pulmonary changes produced by lesions which might be insignificant in the air passages of a child or an adult. The fundamental mechanics of

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these changes found in infants, however, are identical to those found in adults.

The congenital cardiovascular anomalies, which produce obstruction of the lower respiratory tract, may be divided into two major groups: 1) malformations of the heart, and 2) anomalies of the aorta and its main branches.

*Bronchial Obstruction Due to Malformations of the Heart.*—Developmental anomalies of the heart itself, when accompanied by progressive enlargement, may produce serious compression of the tracheobronchial tree. This is illustrated in the following case reports:

CASE 1.—R.B., white male infant, three weeks of age, was admitted to the hospital because of recurring attacks of cyanosis. He had his first cyanotic spell at one week of age. He was then apparently well until the three days prior to entry during which he had had an attack of cyanosis each day. The baby was full term, easily delivered, and there had been no difficulty in starting respirations. He had nursed normally as soon as he was put to the breast, with no evidence of esophageal obstruction. Examination revealed a well-nourished, deeply cyanotic infant with rapid, gasping respirations and intercostal and substernal retractions. Dullness and markedly suppressed breath sounds were noted over the entire left chest, although they were essentially normal on the right; squeaky rhonchi were heard over both lung fields. There was a gallop rhythm and an apical systolic murmur heard just outside the left nipple. Stimulants and oxygen effected no improvement, and the infant expired during the first hospital day.

On postmortem examination the heart was found to fill the greater part of the left chest and to extend into the right. The right heart was dilated and the left ventricle showed marked hypertrophy. An almost complete stenosis of the aortic valve was found which admitted only a small probe. The left main bronchus was completely compressed and flattened by pressure of the enlarged left heart so that the walls were in contact. Areas of atelectasis and emphysema of the left lung were noted on histologic examination. Thus, a congenital aortic stenosis resulted in marked hypertrophy of the left ventricle of the heart with compression of the left main bronchus.

A second type of case in this group illustrates the phenomenon of obstructive emphysema most strikingly. This may be contrasted



Fig. 1, Case 2.—Chest x-ray showing obstructive emphysema of the left lung and pneumonic infiltration in the right upper lung field.

with the previous case in which obstruction of the bronchus was complete and resulted mainly in atelectasis.

CASE 2.—C. G., male, five months of age, had been delivered normally. Congenital heart disease was suspected because a murmur had been heard at birth, although no cyanotic spells occurred before the child went home from the hospital. His respiratory rate had always been above normal, but he presented no other unusual symptoms until he suddenly became extremely cyanotic and dyspneic six days before admission. Following the initial symptoms he became cyanotic on the least effort and was extremely cyanotic when brought to the hospital. Examination revealed a critically ill, cyanotic infant with grunting respirations. Breath sounds were suppressed over the entire left chest with the apex beat of the heart in approximately its normal position; no definite murmurs were noted. There was no wheeze. The right side was essentially normal.

X-ray films of the chest showed an increased translucency of the entire left lung field and a relative density of the right upper lobe (Fig. 1). The heart was displaced somewhat to the right,

especially the upper portion, and there was some rotation of the vessels. It was difficult to find any lung markings in the entire left side, giving rise to the question of a large lung cyst or pneumothorax. The findings were considered to be most consistent with an obstructive emphysema of the left lung, apparently due to a partial obstruction of the left main bronchus, in spite of absence of a wheeze.

A bronchoscopic examination was made with the following findings: "The trachea and right main bronchus were patent and, except for marked cyanosis of all structures, they appeared normal. The left main bronchus was collapsed and seemed to be only a slit. Forceps were inserted, dilating the left main bronchus, and the bronchoscope could then be passed down the left side. During the procedure, there was a definite change in the color of the mucous membrane; it appeared pinker than at the onset of the procedure. It was apparent that the bronchus was compressed from without and that the compression could easily be relieved. The bronchus below the point of obstruction was normal. On removing the bronchoscope the bronchial walls showed no tendency to remain patent and collapsed immediately." Following bronchoscopy, the child seemed slightly improved. His color was definitely better, and breath sounds were heard over the left lower lobe. The following day dyspnea returned and became severe with each feeding. A wheeze developed and he became more cyanotic. His clinical condition deteriorated rapidly, and death ensued on the fourth hospital day.

At postmortem a much dilated right auricle and tremendously dilated auricular appendage were found. There was a tricuspid atresia and hypoplastic right ventricle, patent foramen ovale and patent interventricular septal defect. A transposition of the great vessels was present, with the pulmonary artery arising from the left ventricle and the aorta overriding the interventricular septal defect. The transversely placed, distended right auricular appendage, when expanded with blood, compressed the left main bronchus, the bifurcations of which were resting on the thoracic aorta, with resultant obstructive emphysema of the left upper and lower lobes.

Malformations of the heart, of course, make up the largest and most important group of cardiovascular anomalies from the general clinical standpoint. Enlargement of one or more chambers occurs in a variety of cardiac defects, and it is not within the province of this paper to enumerate or discuss these. These two cases serve to



illustrate the manner in which such cardiac enlargement can produce obstruction of the tracheobronchial tree. Although an admittedly rare event, this mechanism may be responsible for the chief respiratory symptoms at a given stage of the heart disease. Its main significance would appear to lie in including this possibility in the differential diagnosis of respiratory tract obstruction in early life. The presence of a persistent heart murmur would suggest the underlying cardiac condition in most instances. In a few, the basic factor might possibly be overlooked because of indistinct murmurs, absence of signs of frank cardiac failure and normal appearance of the heart on the routine roentgenogram of the chest.

In the first of the two cases described above, progressive cardiac enlargement compressed the left main bronchus to produce atelectasis of the left lower lobe. The diagnosis of bronchial compression was incidental and purely academic, since the extensive cardiac anomaly was obviously incompatible with life. In the second case, the clinical picture was that of a sudden partial obstruction of the left main bronchus causing an extreme obstructive emphysema of the entire left lung. The importance of the pulmonary findings seemed clinically to outweigh the suspected cardiac disease. Bronchoscopy demonstrated the obstruction to be due to extrabronchial pressure, directing attention to the etiologic significance of the cardiac findings. The postmortem examination showed the obstructive emphysema to be due to a transversely placed, distended right auricle compressing the left bronchus against the thoracic aorta.

Tracheobronchial obstruction produced by cardiac anomalies has received little mention in the literature. Bach, Keith and Loud<sup>1</sup> discussed the question of bronchial compression due to auricular dilatation and illustrated their report with a case similar to that presented above (Case 2). It is interesting to note that in their case, however, a complete collapse of the left lung occurred rather than an obstructive emphysema.

Tracheal displacement is often of significance in the analysis of respiratory tract obstruction produced by cardiovascular anomalies. Roessler<sup>2</sup> mentions tracheal deviation produced by congenital cardiac malformations, evaluating its significance as a diagnostic roentgen sign. He stresses the importance of the anterior and lateral views in both the inspiratory and expiratory phases of respiration. He notes a marked buckling and deviation of the trachea to the right at the height of the expiratory phase in the anterior view and some buckling associated with moderate diminution in the caliber of its lumen in the lateral view. Tracheal displacement has, there-

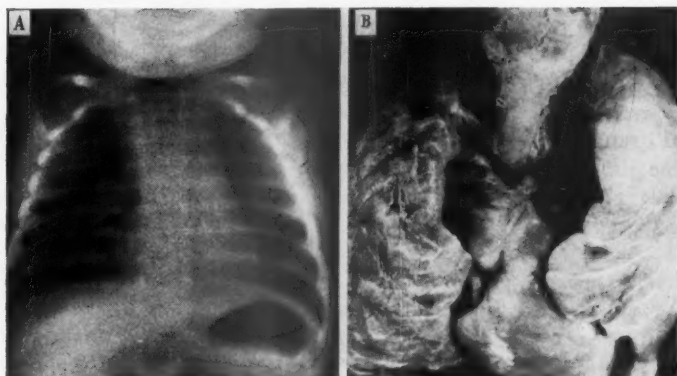


Fig. 2, Case 3.—(A) Chest x-ray showing widening of upper mediastinum. (B) Autopsy specimen showing origin of the double aortic arch and emphysema of the lungs.

fore, pathognomonic significance only when present in the inspiratory phase. A markedly enlarged thymus gland also causes such a displacement. Pendergrass and Allen<sup>3</sup> also mentioned tracheal displacement as a roentgen sign, stressing, too, the importance of the inspiration picture. In 150 normal infants, tracheal displacement did not occur on the inspiratory film while in nine cases of congenital heart disease tracheal displacement was found in the absence of thymic enlargement.

*Tracheobronchial Obstruction Due to Congenital Anomalies of the Aorta and its Main Branches.*—Congenital malformations of the aorta producing tracheobronchial obstruction are not uncommon. Of the various developmental malformations of the aorta, the most frequent cause of respiratory tract obstruction is the double aortic arch or so-called "vascular ring." The clinical aspects of this anomaly in its role as a constricting ring in infants were completely reviewed in a recent report by Gordon.<sup>4</sup> Three of the following series of five cases were previously described in this author's article.

CASE 3.—L. H., male infant, aged 4½ months. The birth weight was 6 lbs., 2 oz., and delivery normal, but the infant had had difficulty in respiration since birth with peculiar grunting sounds, especially when nursing. A diagnosis of an enlarged thymus was made by roentgen-ray examination, the mediastinal shadow be-

ing 3.5 cm. in width. He received four x-ray treatments of 40 r each, with no improvement, and no change was noted in the x-ray picture (Fig. 2A). He was admitted to the hospital because of restlessness, fever, stridor and cough. On physical examination many coarse râles were found in both bases, and he was markedly dyspneic and cyanotic. Dullness, bronchial breathing and bronchophony became pronounced over the right lower chest posteriorly, with the same findings noted in the left chest two days later. Oxygen was given but relief was only temporary. The child died of asphyxia.

The pertinent postmortem findings were as follows: "The heart lies in its customary situation, with the apex in the fifth interspace. It does not seem enlarged. The thymus is small, weighing 5 grams. The aorta leaves the left ventricle in the normal fashion, passing upward, forward, and to the right. About 2 cm. beyond its point of origin it divides into two branches (Fig. 2B), a right and a left, which pass to either side of the trachea and esophagus to reunite posteriorly and form the descending aorta. These pursue a somewhat diagonal course, so that the left branch runs more anteriorly and the right more posteriorly. The diameter of the ascending aorta is 1.2 mm., of the right arch 0.8 mm., and the left arch 6 mm. Just at the bifurcation each gives off the common carotid artery, these two trunks being about 3 mm. apart from each other. A few millimeters behind these, the subclavian arteries arise, and beyond the left subclavian artery, from the under surface of the left branch, the narrow cord of the ductus arteriosus runs down to join the pulmonary artery. Thus the trachea and esophagus are entirely surrounded by an arterial ring, the inner diameter measurement of which is one centimeter. The trachea has a diameter of 1 cm., but becomes somewhat constricted in its transverse diameter while passing through this ring. The esophagus appears normal, although in this region its outer coat is congested. The diameter of the descending aorta in the upper thoracic region is 1 cm. The vocal cords show no evidence of laryngeal stenosis. The trachea and esophagus do not seem dilated above or below the aortic arch."

CASE 4.—M. W., a white female, four months of age, was admitted to The Children's Memorial Hospital on February 21, 1943. Wheezing respirations had been noted since birth. On the fourth day of life, the patient developed two attacks of cyanosis after feeding, and a tentative diagnosis of persistent thymus was made. She began having repeated attacks of vomiting at about two months of age. Two weeks before entry, the patient developed fever, cough, increasing respiratory distress and cyanosis. On admission,

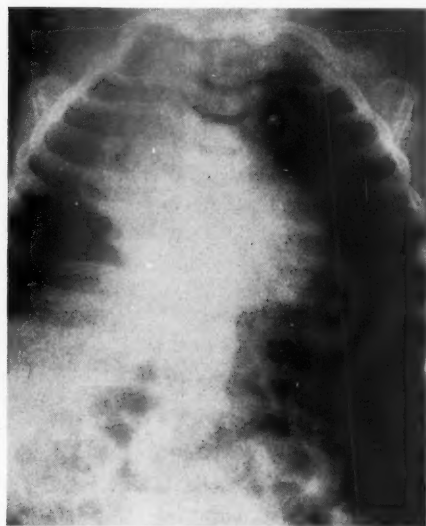


Fig. 3, Case 4.—Chest x-ray showing abnormal density in the right upper lung field.

she appeared moribund with gasping respirations, deep cyanosis, and a temperature of  $106^{\circ}$  F. The entire chest with the exception of the right upper lobe was hyperresonant, and breath sounds were diminished over this area. X-ray film of the chest showed decreased radiolucency of the upper half of the right lung field (Fig. 3). The patient's general condition was considered too critical for bronchoscopy. There was no response to chemotherapy, oxygen, or blood transfusions, and the infant expired on the third hospital day.

The pathological findings were: 1) double aortic arch with left arch partially obliterated; 2) patent ductus arteriosus; 3) pneumonia of the right upper and middle lobes.

CASE 5.—D. M., white female, four months of age, was admitted to The Children's Memorial Hospital November 21, 1942. Noisy respirations had been noted since birth. Five days before entry the patient developed a persistent cough, fever and listlessness. She became comatose on the day of admission and was in a state of collapse when first examined. The skin was cold, pale and

cyanotic. Respirations were rapid and shallow. The chest appeared fixed in inspiration. There was dullness, bronchovesicular breath sounds, and râles noted over the right upper lung field, and diminished breath sounds over the entire left lung. X-ray films of the chest revealed "clouding of the lower two-thirds of the right upper lobe and a considerable portion of the right lower lobe." Bronchoscopy showed partial obstruction of the left main bronchus by external compression from the medial aspect and considerable mucopurulent discharge throughout. Extensive therapy effected no significant improvement, and the child expired on November 25, 1942.

The pathological findings were: 1) double aortic arch with compression of the trachea; 2) emphysema of the left upper lobe; and 3) areas of atelectasis and pneumonia in the remaining lobes of the lung.

CASE 6.—D. Z., a white male infant, aged four months, was admitted to The Children's Memorial Hospital on June 29, 1946. At the age of five weeks the patient began having recurrent attacks of stridorous breathing and cyanosis. At the age of seven weeks he was hospitalized for two months in another institution with the diagnosis of aspiration pneumonia. Shortly after discharge, on June 15, 1946, he developed a recurrence of respiratory distress and was admitted to this hospital. The cyanosis and stridor were increased during feedings. Examination revealed a well-nourished and well-developed infant with crowing respirations and mild intercostal retractions. Breath sounds over the chest were harsh and their expiratory phase prolonged. X-ray films of the chest and neck were reported negative. Bronchoscopy on June 30 revealed marked compression stenosis of the trachea and both main bronchi in the region of the coryna.

Treatment with penicillin and oxygen was instituted, but daily episodes of wheezing, dyspnea and cyanosis continued. X-ray therapy was administered on July 3, 7 and 17, without any apparent effect. Repeat bronchoscopy on July 12 showed unchanged findings. On July 23, the esophagus was visualized with iodochloral, and slight narrowing at the level of the aortic arch was noted. A tentative diagnosis of constricting vascular ring was made, and an exploratory thoracotomy was performed on July 27 by Dr. Willis J. Potts. The heart, aortic arch and great vessels were well-exposed, but the nature of the constriction was not found at operation. The postoperative course was uneventful until the fourth postoperative



Fig. 4, Case 6.—Autopsy specimen viewed from above showing clearly both limbs of the double aortic arch which encircle and constrict the trachea and esophagus. The smaller right limb is situated posteriorly and could not be seen from the anterior view.

day when the patient developed a sudden attack of cyanosis and died within a period of two hours.

The pathological diagnosis was double aortic arch with compression of the trachea and esophagus (Fig. 4). The left limb of the double aorta was of normal size while the right arch was small; since the latter was situated posteriorly, it had been obscured from anterior view on surgical exposure. This is an unusual pattern for this type of anomaly.

CASE 7.—S. W., white male, aged eight years, was first admitted to The Children's Memorial Hospital at the age of three months because of difficult breathing and hoarseness since birth. A diagnosis of congenital laryngeal stridor was made. During the course of the next six years he was admitted to the hospital approximately 30 times because of continued stridor and hoarseness, intermittent wheezing and dyspnea, frequent bouts of respiratory tract infections, and one or two attacks of pneumonia each year (Fig. 5A). Repeated bronchoscopic examinations revealed stenosis of the trachea by pressure from without, about 1.5 cm. above the coryna. In June 1943, a barium swallow revealed a posterior indentation of the esophagus at the level of the arch of the aorta, and a tentative diagnosis of vascular anomaly of the great vessels was made.

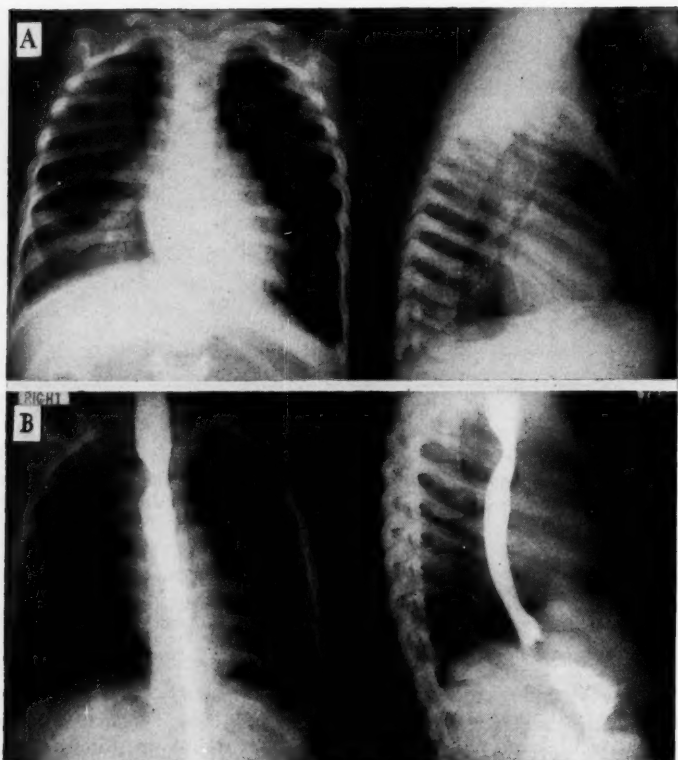


Fig. 5, Case 7.—(A) Chest x-rays of patient at the age of two years showing no apparent abnormality of the heart or great vessels. Infiltrate at right base represents one of repeated attacks of pneumonia. (B) Esophagrams showing posterior and lateral rounded defects at the level of the arch of the aorta.

At the end of 1945 the patient disappeared from observation until September 1947, when he was admitted with an acute upper respiratory infection. His previous respiratory symptoms had remained essentially unchanged. Examination revealed the patient to be underweight but otherwise well developed with slightly stridorous breathing and a paroxysmal, rasping cough. The breath sounds over both sides of the chest were roughened, but no adventitious sounds, other than transient rhonchi, were heard. Further x-ray





Fig. 6, Case 7.—Postoperative lipiodol studies of the trachea and bronchi showing persistent narrowing of the trachea at the level of the aortic arch (retouched print).

films of the esophagus with barium (Fig. 5B) showed the same indentation of the posterior wall as seen in 1943. A diagnosis of double aortic arch was made, and an exploratory thoracotomy was performed on September 25, 1947, by Dr. Willis J. Potts.

At operation a double aortic arch was found encircling the trachea and esophagus. The right and posterior limb was of about normal size, but the left and anterior arch was markedly narrowed. The small anterior limb was divided, relieving the constrictive pressure. The immediate postoperative course was stormy, but thereafter recovery from the operation was uneventful. Respiratory obstruction has not been entirely relieved. Bronchoscopy and bronchograms (Fig. 6) reveal a persistent narrowing above the coryna, and the wheezing and brassy cough, while much improved, are still heard. Bronchoscopic examination further demonstrates the tracheal wall at the point of stenosis to be unusually flaccid, suggesting an absence of cartilage in this region. Dysphagia was quite pronounced before operation. This symptom has entirely disappeared.

Embryologically, the double aortic arch results from a failure of the usual involution of the fetal right fourth aortic root. Both right and left primitive fourth arches persist, forming an arterial ring which encircles the trachea and esophagus. The right and posteriorly placed arch is, as a rule, of normal caliber and larger than the left which is usually partially obliterated. In the majority of instances in which this anomaly is found, the double arch anomaly produces little or no symptomatology and is only discovered as an incidental clinical or postmortem finding. However, in certain individuals in the early age group, it does cause serious compression of the trachea and esophagus.

The clinical findings of this anomaly in infants have been more or less similar in all of the observed cases and have been well described by Wolman<sup>5</sup> and by Herbut and Smith.<sup>6</sup> Symptoms usually become manifest shortly after birth and consist of stridorous breathing, chronic cough, attacks of dyspnea and cyanosis; all made worse by feeding. Slight difficulty in swallowing and frequent respiratory infections have been constant findings in this group. With few exceptions, before the advent of surgery these symptoms lead to death within six months. Case 7 has had the longest life span (eight years) of any known patient with the typical clinical syndrome in early life. Although admittedly a rarity, constricting vascular ring is being recognized with increasing frequency in recent years and must be considered a possible etiologic factor in all infants with symptoms of respiratory tract obstruction.

As is well known, a number of widely different conditions may produce this picture of obstruction in early life. The clinical features may be indistinguishable on the routine examination, and the diagnosis is, therefore, often difficult to establish. Roentgenograms of the chest and neck of infants with a double arch may show no abnormality or they may reveal a widened upper mediastinal shadow without special diagnostic features. Fluoroscopic and radiographic studies of the esophagus aid in visualizing the associated compression of this viscus. At this point in the survey, laryngoscopic and bronchoscopic examinations are invaluable in recognizing and excluding many of the more common causative factors of chronic, progressive respiratory tract obstruction. Such lesions as a flaccid larynx (congenital laryngeal stridor), laryngeal papillomata or webs, congenital pharyngeal or laryngeal cysts, nonopaque foreign bodies, endobronchial tumors and webs depend on the direct examination for their final diagnosis. Discovery of external compression at a particular site may give the first clue to the existence of a vascular ring (Cases

4, 6, 7). The endoscopic findings should suggest any special x-ray studies needed.

Neuhauser<sup>7</sup> mentions the following roentgen changes as characteristic of double arch: 1) narrowing and anterior displacement of the trachea at the level of the aortic arch in the lateral projection; 2) on the esophagram, anterior displacement and rounded defect on the posterior aspect in the lateral view; and narrowing of the esophagus from both the right and left sides on the antero-posterior projection. Angiography which might demonstrate the presence of a vascular ring with even more exactitude has, to our knowledge, not yet been used for this purpose.

Gordon,<sup>4</sup> in her review of the literature, collected 11 cases of constricting double aortic arch in infancy, to which she added three unreported cases from The Children's Memorial Hospital. (The addition of Case 7, described above, makes a total of four encountered in this hospital in the past ten years.) Neuhauser<sup>7</sup> mentions four cases of constricting double arch clinically diagnosed at The Infants' & Children's Hospital in Boston. Snelling and Erb<sup>8</sup> present a case of double aortic arch with clinical, roentgen and anatomical data illustrating this type of anomaly and demonstrating its significance in tracheobronchial obstruction. The difference between this roentgen picture and that of simple right aortic arch is discussed, and a review of embryology and recent literature is given. They state that double aortic arch causes a constriction of the esophagus and trachea and death at an early age results, due possibly to an aspiration bronchopneumonia. An unusual aspect of these phenomena is presented by Herringham and Arkin,<sup>9</sup> who describe a gradual dilatation of the esophagus produced by a double aortic arch with death due to esophageal compression of the trachea and a paralysis of the larynx. Herrmann<sup>10</sup> describes the peculiar wheezing and "dog's bark" cough noted in a case of double aortic arch.

The excellent report of Schall and Johnson<sup>11</sup> illustrates one of the earlier problems of palliative therapy in this type of case. A tracheotomy was performed on a six-month-old infant because of severe respiratory obstruction. Bronchoscopy had demonstrated the obstruction to be tracheal in character, and subsequently a cane tube had to be inserted. Death ensued ten days later from a massive hemorrhage from an erosion into the right aortic arch.

As already mentioned, the prognosis in these infants with symptom-producing double aortic arch was considered hopeless until 1945 when Gross<sup>12</sup> reported on the first patient successfully treated

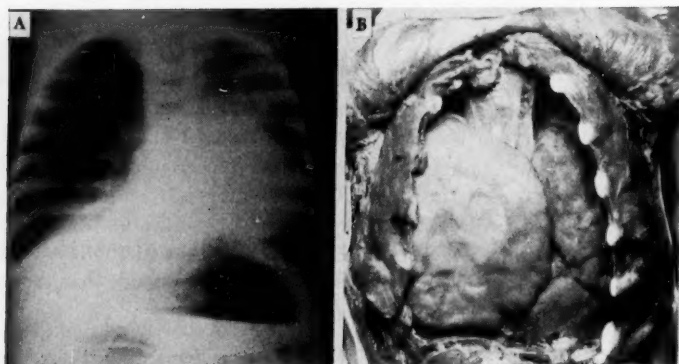


Fig. 7, Case 8.—(A) Chest x-ray demonstrating obstructive emphysema of right lung with displacement of the heart to the left. (B) Postmortem specimen showing marked emphysema of the upper lobe of the right lung.

with surgery. Since that time Gross and Ware<sup>13</sup> have reported an additional case in which the operation was successful. Sweet, Findlay, and Reyersbach,<sup>14</sup> in 1947, described two cases in which the patients were treated surgically with relief. The case mentioned above makes a total of five operated cases to be reported in the past three years.

Another and more common major anomaly of the aorta is the right aortic arch. The following is a case of this type in which compression of the tracheobronchial tree was produced by the defect:

CASE 8.—J. S., white male infant, two months of age, had had difficulty in breathing and attacks of cyanosis since three weeks of age. Physical examination revealed a rather emaciated, cyanotic infant breathing rapidly but with no appreciable indrawing at the suprasternal notch or epigastrium. A marked tympany over the right lung was present on percussion and the heart was found far to the left. The breath sounds were normal on the left but diminished to absent on the right, with occasional wheezing heard loudest on the right side. X-ray films revealed a hyperaerated right lung, depressed right diaphragm, and a shift of the heart to the left, all findings suggesting an obstructive emphysema of the right lung (Fig. 7A). A

bronchoscopic examination demonstrated a compression stenosis of the right main bronchus and a collapsed and distorted right upper lobe bronchus. The infant bronchoscope could be passed through the stenotic right main bronchus with ease, and definite relief of symptoms was noted following each of six bronchoscopies done at intervals of one to two weeks. At times breath sounds were heard over the posterior portion of the right chest and occasionally even over the anterior portion. However, it was necessary to place the child on oxygen frequently, and suddenly after two months of observation he showed a definite change and expired four days later.

Postmortem examination revealed a widespread obstructive emphysema of the right upper lobe, the anterior lappet extending into the left thoracic cavity (Fig. 7B). A stenosis of the right upper lobe bronchus was visualized and at the site of the obstruction the thoracic aorta was found to pass to the right of the trachea instead of to the left, thus compressing the right upper (epi-arterial) bronchus. The bronchus itself was found to contain less cartilage at this point than normal and was compressed to a mere slit. Other significant findings were a focal atelectasis and emphysema of the right lower lobe and a fetal endocarditis.

The right aortic arch anomaly results from a persistence of the embryonic fourth right aortic arch, whereas normally the left primitive arch becomes the aorta. In this anomaly the aorta arches over the right main bronchus and courses downward either to the right of or behind the esophagus. The latter or posterior type is the more common. The right aortic arch, in association with other developmental defects, may assume different forms, of which the following are important with respect to respiratory tract obstruction:

1. Encirclement of the trachea and esophagus. An aberrant ductus or ligamentum arteriosum, by virtue of its attachment to a posterior right arch or to a remnant of the fetal left fourth arch ("aortic diverticulum") may cause backward traction on the pulmonary artery and thereby produce compression of the trachea and esophagus. A constricting ring is thus formed by the aortic arch behind, the ductus on the left, and the pulmonary artery in front. This type of deformity, referred to also as a "vascular ring," is the mechanism most commonly responsible for respiratory tract obstruction in right aortic arch anomalies.

2. Anomalous left common carotid artery. This vessel may arise from the right of the midline and, in crossing to its distribution, may impinge on the anterior surface of the trachea.

3. Anomalous left subclavian artery. With also a right-sided origin, this may cross either behind the esophagus or between the esophagus and the trachea, and cause compression.

The right aortic arch anomalies produce no symptoms in the majority of cases. The most frequently mentioned symptom in the literature has been dysphagia due to pressure on the esophagus. Compression of the tracheobronchial tree has been reported in only a few instances. Snelling and Erb<sup>8</sup> in 1933 mentioned a case of Blackfan's of respiratory distress in a five-month-old infant due to the constricting ring form of right arch. A similar case was reported by Gross and Ware<sup>13</sup> in 1946. Garland<sup>15</sup> in 1938 described an adult with respiratory symptoms due to a simple right-sided aorta. Faber, Hope and Robinson<sup>16</sup> in 1945 reported on two infants with respiratory difficulty due to right aortic arch, but the exact form of the anomaly and the mechanism of obstruction were not determined with certainty since there were no operative or necropsy findings. This subject is further discussed by Blackford, Davenport and Bayley<sup>17</sup> and by Sprague, Ernlund and Albright.<sup>18</sup>

The clinical syndrome of respiratory tract obstruction in infants with the constricting ring of the right arch may be identical with that seen in the double arch. Clear-cut differentiation of the two conditions may be impossible. Obstruction of the right main bronchus, as was demonstrated in the case presented above, has not been previously reported in connection with right arch anomalies. Its occurrence in this one isolated instance cannot be explained.

The diagnosis of right aortic arch can frequently be suspected from the postero-anterior chest film, when the aortic "knob" is not observed in its usual position or when it is noted on the right side, often within the shadow of the superior vena cava. In addition, deviation of the trachea to the left may be detected. According to Neuhauser,<sup>7</sup> the posterior right aortic arch in its various forms is best recognized by esophagrams which show deviation of the esophagus to the left with a rounded defect on its right lateral and posterior aspects. As mentioned previously, in the not too rare case in which there is disabling respiratory tract obstruction, endoscopic measures can be invaluable in differentiating the various possible etiologic factors and establishing the correct diagnosis. With regard to treatment of the symptom-producing right arch anomalies, Gross and Ware<sup>13</sup> have described several possible corrective surgical procedures. No operative cases have yet been reported.

Congenital anomalies of the great vessels, without malformation of the aorta, are occasionally encountered. An anomalous right



subclavian artery, arising as the last branch of a normal aortic arch, must cross the midline from its left-sided origin to gain exit from the chest. It may course between the esophagus and the trachea or in front of the trachea, and the possibility of tracheal compression in such event is mentioned by Gross and Ware.<sup>13</sup> Jackson, in discussion of Schall's<sup>11</sup> paper on congenital aortic anomalies, described an infant with dyspneic attacks found on postmortem to have an anomalous left common carotid artery compressing the trachea. Edwards<sup>19</sup> presented a case of aberrant or right-sided ductus arteriosus in which the pattern of the anomaly was a mirror image of the encircling ring of the right aortic arch. No symptoms of tracheal obstruction, however, were demonstrated in this patient, a 19-month-old child.

Scheid<sup>20</sup> describes a slightly different malformation of the trachea and of the left pulmonary artery with death due to suffocation in a child seven months of age. An excellent review of the literature is found in his article.

It is possible that coarctation of the aorta may produce tracheal or bronchial obstruction as the pressure in the arch of the aorta increases. Respiratory obstruction has never been considered an important feature of this syndrome; however, Hammond, in a further discussion of Schall's<sup>11</sup> paper, presents a case of a three-month-old infant who died of a congenital coarctation of the aorta with fusiform dilatation sufficient to cause a compression of the trachea.

#### SUMMARY

Outstanding achievements in cardiovascular surgery in recent years have given new impetus to the study of congenital cardiovascular anomalies. Certain of these anomalies cause disabling respiratory tract obstruction in early life and these may be divided into two major groups: 1) Malformations of the heart; these were found to be major developmental defects with chamber enlargement to cause compression of the bronchi. 2) Anomalies of the aorta and its main branches. The most common in this group were found to be the double aortic arch and the constricting ring variety of right aortic arch. Representative examples of cases of each category are presented to illustrate the diagnostic and clinical-pathological aspects of this problem.

The clinical findings are often not distinctive and differentiation of obstructing cardiovascular anomalies from other possible



causes of respiratory tract obstruction usually poses a difficult problem. Current writings stress the diagnostic dependence upon roentgenography, yet routine x-ray studies may not reveal any distinctive findings. On the other hand, laryngoscopy and bronchoscopy may be most informative. In the initial phases of investigation, other common causes of tracheobronchial obstruction can be excluded by endoscopic examination and the exact site of compression can often be determined to lead to an early suspicion of a vascular anomaly. The indications for further, more specialized x-ray procedures may then be clarified and fulfilled. The complex nature of the disease and the serious prognosis of the patients in this group justify utilization of every diagnostic aid obtainable.

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## LXIX

### BRONCHOSPIROGRAPHY: INDICATIONS AND TECHNIQUE

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Interest in the clinical application of pulmonary function tests has increased greatly during the past decade; this is particularly true of bronchosprometry, the procedure by which function of the separate lungs may be determined simultaneously. The subject is one which concerns the bronchologist, not only because of his natural interest in bronchopulmonary physiology, but also because he will see many patients in whom function tests are indicated and will undoubtedly be called upon to participate in the procedures by which clinical data are obtained.

It is now generally recognized that determinations, by external spirography, of the combined function of the two lungs are in many cases of limited clinical value. The thoracic surgeon is interested in the ability of the patient to withstand unilateral procedures, and only the simultaneous determination of the functional capacity of the separate lungs will show whether the contralateral lung is capable of assuming what function is lost, temporarily or permanently, on the operated side.

Even the most careful roentgen study cannot be depended upon for a reliable estimate of separate lung function. A lung which appears clear and well aerated on the roentgenogram may prove to be greatly limited in its ventilatory capacity as a result of hilar fixation or healed pleural disease which interferes with the bellows action of the chest wall and diaphragm. On the other hand, a lung in which much abnormal density is evident by x-ray examina-

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tion may prove to have a satisfactory capacity for both ventilation and oxygen absorption.

In principle, the procedures in routine use for external spirometry and bronchospirography are the same. A closed-circuit system, similar to that of the ordinary basal metabolism apparatus, provides for rebreathing of an air-oxygen mixture, the expired gases being directed through a soda-lime filter for absorption of carbon dioxide. The spirographic tracing obtained indicates the amount of gas mixture ventilated with each respiration (*tidal volume*); *vital capacity* is recorded from the end of the deepest possible inspiration to the end of the greatest possible expiration. *Maximum breathing capacity* is obtained by having the subject breathe as deeply and as rapidly as possible for a brief period, usually about one-half minute. *Ventilation reserve*, a measure of the subject's ability to increase his ventilation above basal requirements, is calculated by

the formula 
$$\frac{\text{Maximum Breathing Capacity} - \text{Minute Volume}}{\text{Maximum Breathing Capacity}} \times 100,$$

in which *minute volume* is the amount of mixture ventilated per minute under approximately basal conditions.

The *rate of oxygen absorption* is calculated directly from the slope of the curve. *Ventilation equivalent*, a measure of the efficiency of alveolar ventilation and oxygen absorption, is the number of liters of gas mixture which must be ventilated to allow absorption of 100 ml. of oxygen. This figure, however, must be interpreted with some caution, since it represents an attempt to correlate a physicochemical process (oxygen absorption) with one which is controlled by nervous and humoral mechanisms which are variable (ventilation).

The bronchospirographic tracings, recorded simultaneously for the two lungs on a "twin spirometer" are analyzed in essentially the same way as the spirographic tracing. Tidal volume, minute volume, vital capacity and rate of oxygen absorption are recorded for the separate lungs. Accuracy of determinations of the maximum breathing capacity for the two lungs, if read directly from the bronchospirographic tracing, is questionable because of the increased and unequal resistance to air exchange. However, if it may be assumed that the ratio of the separate vital capacities represents the relative ability of the two lungs to increase their ventilation, then the values for the individual vital capacities and the value for maximum breathing capacity obtained on external spirometry may be

used in estimating the separate maximum breathing capacities, as follows:

$$\text{M.B.C. Right} = \frac{\text{V.C. Right}}{\text{V.C. Right} + \text{V.C. Left}} \times \text{M.B.C. External.}$$

Ventilation reserves for the separate lungs calculated by the formula

$$\frac{\text{M.B.C. Right} - \text{M.V. Right}}{\text{M.B.C. Right}} \times 100 \text{ are not valid because of the fact}$$

that in bronchspirometry the separate minute volumes are recorded under varying degrees of physical stress, rather than under basal conditions. A reasonably close estimate of the separate ventilation reserves may be obtained, however, as

$$\left(1 - \frac{\text{M.V. \% Right} \times \text{M.V. External}}{\text{V.C. \% Right} \times \text{M.B.C. External}}\right) \times 100,$$

$$\text{where M.V. \% Right is } \frac{\text{M.V. Right}}{\text{M.V. Right} + \text{M.V. Left}} \times 100$$

$$\text{and V.C. \% Right is } \frac{\text{V.C. Right}}{\text{V.C. Right} + \text{V.C. Left}} \times 100.$$

This calculation, too, assumes that the separate vital capacities indicate the relative ability of the two lungs to increase ventilation. Approximate normal values for the data obtained on routine spirometry and bronchspirometry are listed in Table 1.

*Indications.*—Broadly speaking, determination of function of the separate lungs may be indicated in any case of chronic chest disease where a contemplated procedure will result in temporary or permanent impairment of pulmonary function. In practical application, bronchspirometry is appropriate in certain cases of both tuberculous and nontuberculous disease.

*Pulmonary Tuberculosis.* The selection of some form of irreversible collapse therapy in a given case of pulmonary tuberculosis implies some assurance that the contralateral lung will be capable of compensatory function. Frequently, the presence of healed or active disease will raise a question as to its ability to compensate for further loss of function of the lung to be collapsed. The fallacy of attempting to estimate this compensatory ability by roentgen study, with or without the data obtained on external spirometry, has been shown by a number of authors, notably Jacobaeus and associates,<sup>8,9</sup> Cournand and his associates,<sup>3,4</sup> and Leiner, Pinner and

TABLE 1.  
DATA OBTAINED ROUTINELY ON EXTERNAL SPIROGRAPHY AND BRONCHOSPIROGRAPHY  
(APPROXIMATE NORMAL VALUES FOR A HEALTHY ADULT OF AVERAGE SIZE)

VENTILATION				
	RIGHT LUNG	LEFT LUNG	EXTERNAL	
Tidal Volume (T.V.)	125 - 500 ml.	125 - 500 ml.	250 - 1000 ml.	
Minute Volume (M.V.)	2000 - 4000 ml.	2000 - 4000 ml.	4000 - 8000 ml.	
M.V. in % of Total	53%	47%		
Vital Capacity (V.C.)	1500 - 2500 ml.	1500 - 2500 ml.	3000 - 5000 ml.	
V.C. in % of Total	53%	47%		
Max. Breathing Capacity (M.B.C.)	10 - 50 L./min.	10 - 50 L./min.	20 - 100 L./min.	
Ventilation Reserve (V.R.)	75 - 90	75 - 90	75 - 90	
ALVEOLORESPIRATION				
Oxygen Absorption/min.	75 - 150 ml.	75 - 150 ml.	150 - 300 ml.	
Oxygen in % of Total	53%	47%		

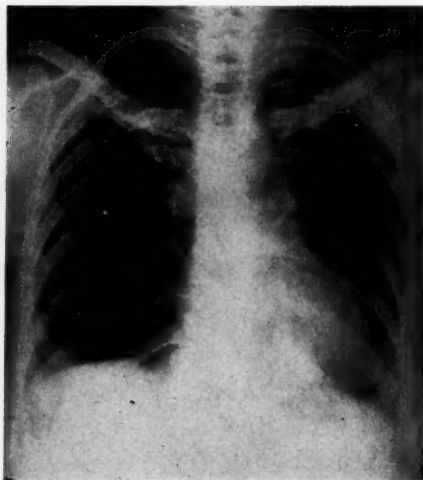


Fig. 1, Case 1.—Bilateral pulmonary tuberculosis; atelectasis of large portion of the right upper lobe and large cavity of the left upper lobe. Pneumothorax on the left was abandoned because of failure to compress cavity; thoracoplasty indicated. Bronchospirography showed adequate compensatory function on the right despite atelectasis in upper lobe.

Zavod.<sup>11, 13</sup> It has been demonstrated that even in cases in which the disease is predominantly on the side to be collapsed, it cannot be assumed that the function of the contralateral lung, though the roentgen appearance is satisfactory, will be normal. Ventilatory function of the contralateral lung may be impaired as a result of mechanical factors interfering with bellows action (pleural synthesis due to previous pneumothorax or healed disease, hilar fixation, phrenic weakness or paralysis), because of emphysema or loss of lung elasticity due to fibrosis or healed parenchymal disease, or as a result of obstructive lesions impairing air exchange. Oxygen absorption may be diminished as a result of inadequate ventilation (due to one or a combination of the above factors), parenchymal disease, or deficient pulmonary circulation.

CASE 1.—H. M., 32 years, had been under sanatorium care for pulmonary tuberculosis for nearly two years. The original roentgenograms showed apparently active lesions in both upper lobes, and sputum had been continuously positive. Serial films demonstrated progressive volume loss of the right upper lobe with diminution in the size of the small cavities originally present. However, progressive enlargement of a cavity in the left upper lobe was observed; pneu-



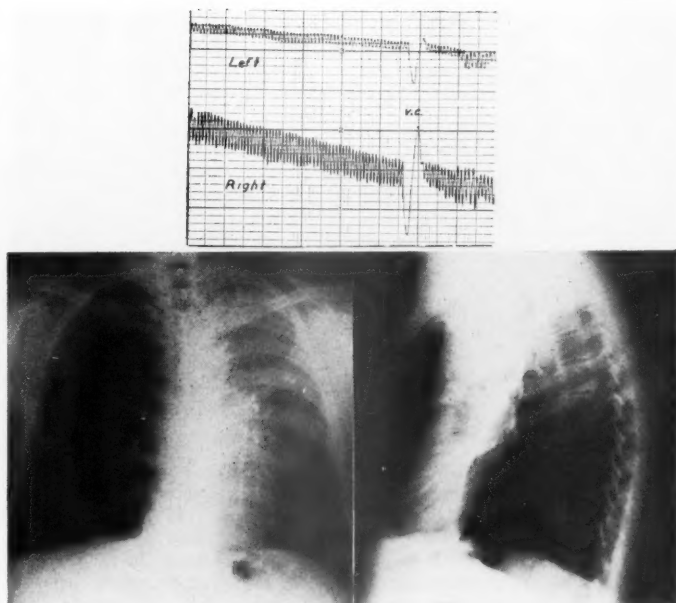


Fig. 2, Case 2.—Bronchogenic carcinoma with atelectasis of the left upper lobe; emphysema (?) of the right lung. A portion of the bronchospirographic tracing indicating satisfactory compensatory function on the right is shown. Pneumonectomy; recovery.

mothorax over a period of seven months failed to compress the cavity and was abandoned (Fig. 1). Thoracoplasty was thought to be the indicated treatment, provided function of the right lung, in spite of the atelectatic upper lobe, proved to be adequate. The over-all ventilation reserve, determined by external spirometry, was 79 per cent; bronchospirography showed distribution of oxygen between the right and left lungs in the ratio of 66 per cent to 34 per cent. Two stages of the thoracoplasty have been completed without untoward postoperative effect.

**Bronchogenic Carcinoma.** In estimating the operative risk of pneumonectomy, the functional capacity of the contralateral lung is of importance. Many of these patients are in an age group where some impairment of the combined cardiopulmonary function is expected apart from that related to the lesion. In addition to the data obtained by external spirometry and bronchospirography, an "overload test"<sup>14</sup> is helpful in detecting cases in which postoperative cardiac insufficiency may be anticipated.



Fig. 3, Case 3.—Advanced bilateral saccular bronchiectasis. (a) Bronchogram of right lung, lateral view, showing involvement of all segments of the right lower lobe, except the superior. (b) Bronchogram of left lung, right anterior oblique view, showing saccular bronchiectasis in lingular portion of the left upper lobe and entire lower lobe. Over-all ventilation reserve considerably diminished (58%). Bronchospirography demonstrated remaining function predominantly on right. Lobectomy (left lower lobe and lingula of left upper lobe); recovery.

CASE 2.—F. J., 57 years, complained of chronic nonproductive cough of ten months' duration, with some dyspnea on exertion. He had been a hard coal miner for many years. Roentgenograms (Fig. 2) showed atelectasis of the left upper lobe, ultimately proven to be due to squamous cell carcinoma of the left upper lobe bronchus, with some emphysema of the right lung. The over-all ventilation reserve as determined by external spirometry was at the lower limit of normal (74 per cent); however, bronchospirography showed the right lung accounting for 74 per cent of the total oxygen absorption (see Table 2 for additional data). Left pneumonectomy (Dr. W. Emory Burnett) was followed by a satisfactory convalescence; no undue dyspnea was observed in the postoperative period.

**Bronchiectasis.** In patients with unilateral bronchiectasis being considered for lobectomy, segmental lobectomy or pneumonectomy, it is unusual to find an unexpected impairment of the functional capacity of the contralateral lung. Determination of separate lung function becomes of great importance, however, in bilateral cases if resection is contemplated. In these cases there may be considerable impairment of function of the combined lungs as determined by external spirometry. An estimate of the ability of the patient to withstand operation on the one side (usually the side of greatest involvement) requires careful study of the bronchospirographic

TABLE 2.  
SPIROGRAPHIC AND BRONCHOSPIROGRAPHIC DATA IN CASE 2 (FIG. 2)

VENTILATION	RIGHT LUNG	LEFT LUNG	EXTERNAL
Tidal Volume	400 ml.	115 ml.	550 ml.
Minute Volume	9200 ml.	2600 ml.	9900 ml.
M.V. in % of Total	78%	22%	
Vital Capacity	1375 ml.	575 ml.	2300 ml.
V.C. in % of Total	71%	29%	
Max. Breathing Capacity	27.5 L./min.	11.5 L./min.	39.0 L./min.
Ventilation Reserve	72	81	74
ALVEOLORESPIRATION			
Oxygen Absorption / min.	223 ml.	75 ml.	276 ml.
Oxygen in % of Total	74%	26%	

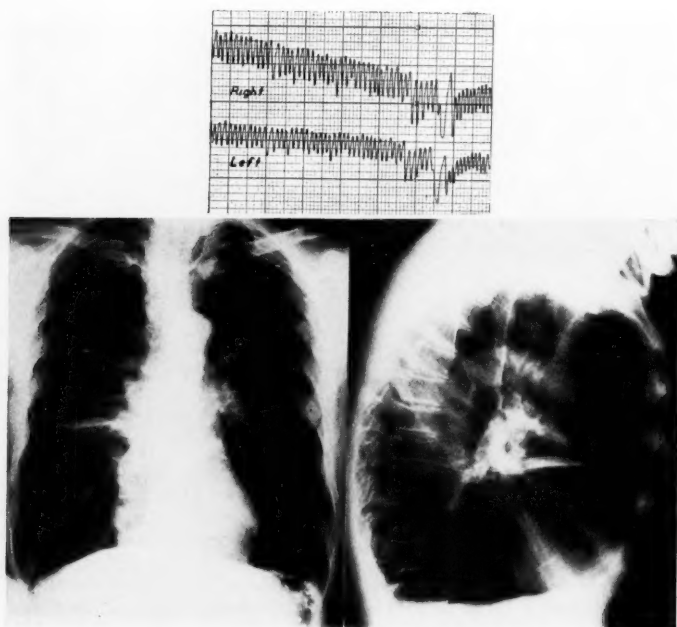


Fig. 4, Case 4.—White male, 58 years; dyspnea increasing over period of several years. Large air-filled cyst-like areas (advanced bullous emphysema) of nearly equal size appear in the two lower lobes. Marked reduction in over-all ventilation reserve (53%); data obtained from the bronchospirographic tracing showed remaining function predominantly on the right. Surgical removal of localized bullous areas on left advised.

data. If, after a suitable interval following the first operation, resection on the opposite side is considered, further bronchospirographic study will demonstrate the functional capacity of the remaining parenchyma on the side of the first operation.

CASE 3.—S. O., 30 years, complained of chronic cough with expectoration of large amounts of odorous, yellowish-green sputum, with blood-streaking at times. The symptoms had been present since childhood following three episodes of "pneumonia." Bronchoscopy showed large amounts of thick purulent secretion, particularly on the left side, but no bronchial lesion other than diffuse mucosal congestion. Bronchography (Fig. 3) showed advanced saccular bronchiectasis of the left lower lobe and the lingular portion of the left upper lobe; similar changes were observed in the right lower lobe.

Because of the bilateral distribution of the bronchiectasis and because of the presence of dyspnea on more than slight exertion, lobectomy had previously

been decided against. The over-all ventilation reserve was greatly diminished (58 per cent). However, bronchospirography showed oxygen absorption distributed between the right and left lungs in the ratio of 70 per cent to 30 per cent. The left lower lobe and lingular portion of the left upper lobe were removed (Dr. W. Emory Burnett). Following a satisfactory convalescence, cough and expectoration were greatly diminished despite remaining bronchiectasis in the right lower lobe, and effort capacity was considerably improved.

**Localized Bullous Emphysema.** In cases of advanced localized bullous emphysema ("air cyst"), in which dyspnea is the usual chief complaint, impairment of ventilatory function is frequently the result of compression of functioning lung parenchyma by large over-distended bullae which in themselves have little or no function in absorbing oxygen. Removal of the bullous portions of lung will allow re-expansion and increased function of the previously compressed parenchyma. However, the estimation of operative risk is a difficult problem, and the data obtained on both external spirometry and bronchospirography must be carefully analyzed because of the accompanying generalized emphysema which is nearly always present. In this group of cases, determinations of residual air and pulmonary emptying rate are of importance.

CASE 4.—J. S., 58 years, complained of dyspnea, which had increased over a period of several years to the point of almost complete incapacity. The roentgenograms (Fig. 4) showed large air-filled cyst-like areas of about the same size in the lower portions of the two lungs. The over-all ventilation reserve was very low (53 per cent), but bronchospirography showed that 68 per cent of the oxygen-absorbing function was on the right (see additional data in Table 3).

In this case, the only available treatment appeared to be surgical removal of the localized bullous areas. The considerable risk appeared justified in view of the progressive nature of the disease. The bronchospirographic finding of remaining function predominately on the right indicates that the left side should be chosen for operation, with the expectation of rather prompt increase in functional capacity as the compressed portion of left lung is allowed to expand following operation. The patient has been so advised, but has not yet consented to operation.

**Other Indications.** In addition to the above indications, mention should be made of the value of bronchospirographic data in studying the mechanisms by which compensation for lost function occurs following collapse therapy or resection. Evaluation of these mechanisms requires not only the routine external spirometry and bronchospirography by closed-circuit methods, but also determinations of residual air, functional residual air, dead space, alveolar concentrations of oxygen and carbon dioxide, and pulmonary emptying time. The studies of Pinner, Leiner and Zavod<sup>13</sup> relating to functional capacity of lungs following thoracoplasty and pneumothorax illustrate this application of bronchospirography. Data ob-

TABLE 3.  
SPIROGRAPHIC AND BRONCHOSPIROGRAPHIC DATA IN CASE 4 (FIG. 4)

VENTILATION	RIGHT LUNG		LEFT LUNG		EXTERNAL
Tidal Volume	375 ml.		275 ml.		525 ml.
Minute Volume	5600 ml.		4100 ml.		9000 ml.
M.V. in % of Total	58%		42%		
Vital Capacity	840 ml.		625 ml.		1600 ml.
V.C. in % of Total	57%		43%		
Maximum Breathing Capacity	10.8 L./min.		8.2 L./min.		19.0 L./min.
Ventilation Reserve	52		54		53
ALVEOLORESPIRATION					
Oxygen Absorption / min.	215 ml.		100 ml.		133 ml.
Oxygen in % of Total	68%		32%		

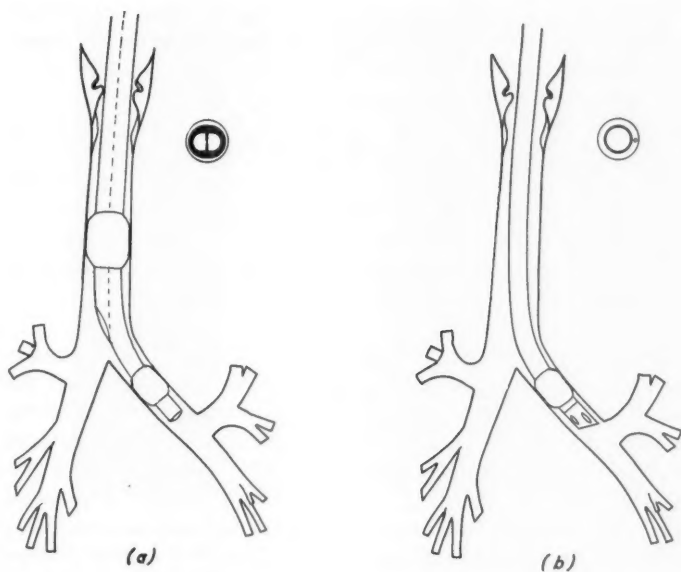


Fig. 5.—Bronchospirography by (a) double-lumen and (b) single-lumen catheter methods. The smaller sketches, made to scale, compare in cross section the available lumina for air exchange to the separate lungs. Increased resistance of the double-lumen catheter (resulting in "stenosis breathing") is largely eliminated when the single-lumen catheter is employed.

tained by bronchospirography during nitrogen respiration of one lung<sup>10, 17</sup> and during respiration of low oxygen mixtures<sup>10</sup> have been used to study separate lung function.

Contraindications to the procedure of bronchospirography are few. Instrumentation is inadvisable in the presence of laryngeal tuberculosis, or tuberculosis of the trachea or the left bronchus, which, if present, will have been noted on indirect laryngoscopy or bronchoscopy. Lesions of the left bronchus (tumor, stenosis or marked distortion) will interfere with positioning of the catheter. Dyspnea of moderate or greater degree is a relative contraindication, depending on the importance of the procedure in a given case. Secretions, if large in amount or of viscid character, may be aspirated through the single-lumen catheter by means of a small caliber rubber tube.



*Technique.*—The first large group of determinations of separate lung function in human subjects was made by Frenckner and Bjorkman,<sup>5,9</sup> working in the clinic of Jacobaeus. The apparatus was a rigid double-lumen bronchoscope, introduced under direct vision and so positioned that air exchange to the two lungs was maintained through the respective channels of the bronchoscope; ventilation and oxygen absorption of the two lungs were recorded simultaneously. Brighton,<sup>2</sup> in 1938, reported his experiences with this apparatus. Bezancon and his associates<sup>1</sup> made a number of observations, using a single-lumen bronchoscope, recording data first from one lung and then from the other.

Gebauer<sup>6</sup> in 1939 and Zavod<sup>18</sup> in 1940 described flexible double-lumen catheters which in some ways simplified the procedure, and Gebauer<sup>7</sup> devised a "twin spirometer" to facilitate simultaneous recording of tracings. The usefulness of the double-lumen catheter is limited by the small size of the breathing channels which it provides (Fig. 5). A breathing mixture rich in oxygen is required, and in spite of this, the increased respiratory effort entailed in "stenosis breathing" may amount to moderate or severe dyspnea sufficient to interfere with completion of the test. Such a situation is likely to be encountered in cases in which the function is predominantly on one side and in cases in which the ventilation reserve of the combined lungs is poor. Furthermore, it is believed that in cases in which there is a marked disproportion between the ventilation of the two lungs, air exchange to the "good" lung is more restricted than that to the "poor" lung. If this is true, then determinations of the relative ventilation of the two lungs will be in error.

We have described elsewhere,<sup>12</sup> a single-lumen catheter for use in simultaneous determination of separate lung function. The method, shown schematically in Fig. 5, makes use of a large percentage of the breathing space available in the natural air passages and largely eliminates the undesirable effects of stenosis breathing. The size most frequently used (26 F.) offers a calculated resistance to air flow which is approximately one fifth of that offered by one channel of the larger size double-lumen catheter. (Resistance to flow of gases through tubes varies inversely with the fourth power of their respective internal diameters.) The lumen of the catheter provides an airway to the left lung, and air exchange to the right lung is maintained around the catheter and through the larynx which, if well anesthetized, does not interfere with free inspiration and expiration.



Fig. 6.—Bronchospirography by the single-lumen catheter method. The flexible catheter is introduced on a heavy wire stilette under guidance of the laryngeal mirror.



Fig. 7.—After positioning under fluoroscopic guidance and inflation of the distal cuff in the left main bronchus, the lubricated outer end of the catheter is brought through a Connell mask and through the rubber diaphragm occluding one arm of the Y-connector. Air exchange to the right lung is then maintained around the catheter, via the other arm of the Y-connector.

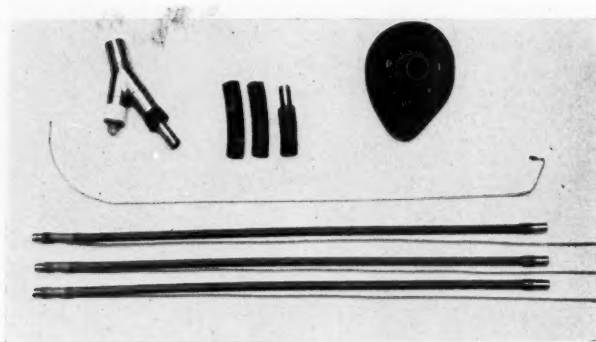


Fig. 8.—Bronchospirography by the single-lumen catheter method. Essential apparatus, including catheters, stilette for introduction, Connell mask, Heidebrinck Y-connector and connecting tubes. Not shown are the equipment for topical anesthesia and the "twin spirometer" on which the tracing is recorded. The flexible catheters, 55 cm. long, 22-26 F., with distal inflatable cuff, are of metal spiral construction, with a short beveled tip providing additional lateral breathing holes. The catheters are sheathed in latex Penrose tubing which is removed after use; another sheath is applied after the catheter has been sterilized by boiling or autoclaving.

Premedication and topical anesthesia are the same as those employed for lipiodol bronchography. The subject is given sodium pentobarbital, 0.1 gm., with atropine sulfate, 0.00065 gm., both by mouth, about one hour before the procedure. The pharynx is sprayed lightly several times with a 2% solution of pontocaine hydrobromide. The larynx, trachea and larger bronchi are then anesthetized by fractional instillation of about 2.0 ml. of the same solution under mirror guidance, using a Lukens syringe and favoring gravitation into the left bronchus by having the patient incline his body to the left and slightly forward after each instillation.

The bronchospirographic catheter is introduced on a curved stilette (Fig. 6) under mirror guidance and then, with the patient supine, advanced into the left bronchus while observed fluoroscopically. The lubricated outer end of the catheter is then brought through a Connell mask and through the thin rubber diaphragm (latex Penrose tubing) stretched over one arm of the Heidebrinck Y - connector (Fig. 7). Air exchange to the right lung is via the other arm of the Y - connector. The shortest possible lengths of large caliber rubber tubing are used to make connection with the spirometers for the respective lungs. Quiet breathing is recorded

for a period of at least four minutes, following which vital capacity for the two lungs is measured; two or three determinations of the latter are desirable.

#### DISCUSSION

The data obtained by the routine procedure as described will in nearly all cases be found adequate for the intended purpose of preoperative evaluation of the relative function of the separate lungs. It should be recognized that in cases where more complete study of the pulmonary function is required, there are available, in addition to the routine data listed above, a number of determinations by methods other than closed-circuit spirometry and bronchospirometry. Determinations of residual air, functional residual air, dead space, alveolar concentrations of oxygen and carbon dioxide and pulmonary emptying time entail the use of other techniques including gas analysis. Such data are of particular importance in the study of cases of diffuse bilateral pulmonary disease, such as nonspecific pulmonary fibrosis, emphysema and pneumoconiosis, conditions in which an estimation of the separate function of the two lungs is not often relevant. Determinations of arterial oxygen and carbon dioxide tensions before and after exercise are of value in any case where the combined cardiopulmonary function is being studied.

The data obtained by bronchospirometry are intended to supplement, and should not be regarded as displacing in importance, the information obtained by external spirometry, in which the combined function of the two lungs is recorded. As has been implied, the chief value of the procedure is in allowing an estimate of the ratio in which the separate lungs participate in the various phases of total function.

The alterations in "dead space" which occur during bronchospirometry by either the single-lumen catheter or the double-lumen catheter method might be considered as a possible source of error. However, data obtained in apparently normal individuals, without evidence of parenchymal or pleural disease, show no variation from the expected ratios for either ventilation or oxygen absorption. The effect of increased oxygen content of the breathing mixture in cases in which the alveolar oxygen is initially below normal (as a result of poor ventilation or poor alveolar mixing) is as yet not determined. Presumably, however, if there is no initial oxygen deficit, the increased percentage of oxygen in the breathing mixture will have little or no effect on the data obtained.

## SUMMARY

1. The principles involved in closed-circuit spirometry and bronchospirography and the data obtainable by these procedures are briefly discussed.

2. The value of bronchospirographic study, when a contemplated surgical procedure may require compensatory function of the contralateral lung, is illustrated by representative cases of pulmonary tuberculosis, bronchogenic carcinoma, bronchiectasis and localized bullous emphysema.

3. The single-lumen catheter technique of bronchospirography and its advantages are described.

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## ESOPHAGEAL HIATAL HERNIA

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The diaphragm has only one normal opening through which gastric herniation is likely to occur. This is the esophageal passage-way which is the weakest point in the diaphragm. Both the vena cava and the aorta traverse the diaphragm, but these vessels fill their openings so completely that hernia is prevented.

The term esophageal hiatal hernia should be reserved for the type of lesion in which the stomach has herniated from the abdominal cavity through the esophageal opening into the thorax, forming a sliding type of hernia with a covering of pleura, peritoneum, or both. The distinction between para-esophageal hernia and true hiatal hernia is that in the former the lower end of the esophagus remains fixed in its normal position and a portion of the stomach herniates through the hiatal ring adjacent to the esophagus, while in the true hiatal type there is protrusion of both the lower end of the esophagus and a portion of the stomach into the thorax.

Congenital short esophagus differs from hiatal hernia in that there is not sufficient esophageal length to allow the stomach to reach the diaphragm, hence the stomach occupies its embryonic thoracic position, having never descended into the abdominal cavity. The length of the esophagus affords the main difference between congenital short esophagus and herniation through the hiatus esophageus.

Esophageal hiatal hernia of the sliding type is the commonest type of nontraumatic diaphragmatic hernia. In Harrington's<sup>1</sup> series of 404 cases of nontraumatic diaphragmatic hernia, 71 per cent were of the esophageal hiatal type. Second in frequency was the congenitally short esophagus, comprising 8 per cent of the total number of cases.

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The amount of mechanical interference with the function of the stomach, the degree of diaphragmatic dysfunction and the amount of increased intrathoracic pressure determine the type and number of symptoms. The variety of symptoms produced may easily confuse the diagnosis when dependency is placed on subjective manifestations. Instead of the many symptoms that commonly are present, there may be no complaints at all. Congenital short esophagus, hiatal hernia and para-esophageal hernia give rise to similar complaints. The complaints may suggest peptic ulcer, coronary occlusion, cardiospasm, intestinal obstruction, gall stones, or cancer. In Ohler and Ritvo's<sup>2</sup> series of 104 uncomplicated cases, 59 presented predominantly gastro-intestinal symptoms, 23 suggested gall bladder disease, 13 simulated coronary disease and 9 were asymptomatic. The size of the hernia does not govern the symptoms, for small hernias often cause more distress than large ones.

In my experience, dysphagia is the most frequent complaint and may be accompanied by anorexia, nausea, vomiting or regurgitation. Swallowing difficulty is usually noticed with solid foods and lodgment not infrequently results, so that the patients find it necessary to take large quantities of fluids with meals. A sensation of food sticking, particularly in the neck region, is a frequent observation. Regurgitation occurs after food intake and may interrupt the course of a meal.

"Food fear" may be present because the patient fears the initiation of an attack of epigastric discomfort. The subsequent restriction of diet with vomiting results in weight loss. Pain, either precordial or radiating upward into the shoulder or downward into the abdomen, is sometimes the first symptom. The radiating chest pain with palpitation and rapid pulse usually comes on during or after a heavy meal and can be relieved by belching of gas or vomiting. Relief by belching or vomiting is rarely accomplished because the pressure of the herniated stomach on the lower end of the esophagus interferes with eructation and regurgitation. When spasm of the diaphragm develops, phrenic pain referred to the top of the shoulder occurs.

Increased intrathoracic pressure and interference with diaphragmatic motion cause cardiac embarrassment and dyspnea. Aggravation of symptoms takes place when the patient is prone, and breathing becomes easier in the erect position. The epigastric distress varies from a few minutes to hours with a corresponding inconstancy in the time interval. In the beginning, the attacks are usually mild and spaced at infrequent intervals, but, as the stomach

becomes fixed by adhesions in the thorax, the attacks become constant and more severe.

Hemorrhage due to ulceration occurs at times, though seldom does it become copious or alarming. Bleeding is present more often in cases of congenital short esophagus than hiatal hernia.

Exact roentgen determination of the esophagogastric junction is essential. When an abnormality of the lower end of the esophagus is demonstrable, the esophagus and stomach must be viewed from many angles to determine the position of the lower end of the esophagus, for it may lie behind or to one side of the stomach. The gas bubble below the diaphragm is frequently absent with the patient erect, and use of the recumbent position may be necessary to outline the fundus of the stomach and the lower esophagus. In acquired hernia through the esophageal hiatus the stomach may assume a thoracic position only when the patient is recumbent. Usually the portion of the stomach located in the thorax is wider than the esophagus and is best seen with the patient in the right oblique prone position. The hiatus appears above the position which the lower end of the esophagus would normally occupy. The "pinch-cock" appearance at the hiatus is absent, but the esophagogastric junction can usually be distinguished. Some narrowing at the esophagogastric junction may be observed. When gastric rugae are demonstrated above the diaphragm, the diagnosis becomes certain. When both the lower end of the esophagus and a portion of stomach are located above the diaphragm level, recognition is relatively easy. The diagnosis is more difficult when the esophagus reaches the level of the diaphragm with the herniated stomach extending along the course of the esophagus into the thorax.

A striking and constant feature of acquired hiatal hernia on esophagoscopy examination is the redundancy of the mucosal folds, in contrast to congenital short esophagus where the esophagus is tense on a stretch and the mucosal folds are smooth. With a mobile lower end, the esophagus is shortened, giving rise to mucosal redundancy and appearance of dilatation of the lumen. The redundant folds at the lower end of the esophagus may hinder passage of the esophagoscope into the stomach and, at times, extend into the thoracic esophagus. Measurements from the upper alveolar margin or projection externally on the chest wall, using an applicator to localize the junction of the esophagus and the stomach, confirm the presence of the stomach above the diaphragm, the average length of the adult esophagus from the incisor teeth to the stomach being 40 cm.

After passage of the esophagoscope through the thoracic portion of the stomach, there is an absence of the normal narrowing at the esophagogastric junction. The hiatus is relaxed, wide open and the stomach readily visualized and entered.

At times, narrowing at the esophagogastric junction is observed. The stenosis varies, consisting of either a funnel-like narrowing, an abrupt constriction or a weblike stenosis. The constriction does not resemble the normal sphincteric tightening at the hiatus esophageus but offers greater resistance.

Ulceration varying from a small area at the point of stenosis to extensive change covering the entire stenotic lesion is sometimes found. The ulceration is superficial, covered by a thin grayish exudate, and surrounded by a narrow inflammatory zone. Biopsy of the ulceration is a routine procedure and usually reveals gastric mucosa, but persistent ulceration requires repeated histologic examinations. Sweet<sup>3</sup> has commented on the frequency of carcinoma associated with congenital short esophagus. Granulations, when present, are flat and do not project greatly into the lumen.

Evidence of a moderate degree of chronic esophagitis with some retention in the esophagus may be present.

Simple relaxation of the lower end of the esophagus has not been observed frequently but probably represents the first step in the formation of a hiatal hernia. It results from weakening of the muscle fibers about the hiatus. I believe every case in which relaxation is present should be considered a potential case of hiatal hernia.

The anatomic presence of a portion of stomach above the diaphragm, the absence of the normal hiatal "pinch-cock" action and relaxation of the esophageal mucosa are indicative of hiatal esophageal hernia.

The treatment is surgical if this can be done without serious risk to the patient. The disease is progressive with increasing severity of symptoms, so that if an operation can be performed it should be done while the patient is in optimum operative condition. Surgery aims at replacing the stomach in the abdomen with repair of the relaxed hiatal ring, while other methods of treatment attempt to alleviate the symptoms. The surgical treatment of esophageal hiatal hernia includes phrenic exeresis and surgical repair of the diaphragmatic opening, either singly or in combination. In patients who are poor operative risks, phrenic exeresis alone is used to relieve those symptoms caused by obstruction and strangulation. Surgical repair is difficult when the esophagus will not reach below the dia-

phragm level, and elevation of the diaphragm above the esophago-gastric junction is frequently followed by recurrence. In patients with acquired hiatal hernia who are not suitable for operation and in patients with congenital short esophagus, mechanical, medical and dietetic measures are advocated.

The principles involved in mechanical treatment are relief of obstruction by dilatation and treatment of ulceration by topical application. Relief can be afforded by endoscopic procedures, and patients may be carried along by this means for many years. Dilatation of obstruction can be done either esophagoscopically or perorally by passage of olive-tipped bougies over a previously swallowed string. When the chief difficulty is obstruction alone, repeated peroral bouginage over a previously swallowed string has enabled patients to get adequate nourishment with freedom from dysphagia. In cases with ulceration, treatment must be performed esophagoscopically so that the ulcerated areas may receive local treatment. The use of silver nitrate in 10 per cent solution has proved adequate in promoting healing.

Antispasmodics and alkalis are helpful in relieving symptoms. Postural measures should also be advocated to encourage the passage of food, and the patient usually improves when the semirecumbent position is used for sleeping. Constrictions about the abdomen tend to increase the intra-abdominal pressure and intensify the symptoms. Avoidance of bulky foods, thorough chewing and swallowing small amounts at a time are helpful. Liquids taken during the course of a meal aid in washing down the bolus of food, particularly if there is a tendency for stagnation to occur at the site of herniation.

#### SUMMARY

Acquired esophageal hiatal hernia is the commonest type of nontraumatic diaphragmatic hernia. The symptoms are usually multiple and depend upon the amount of mechanical interference with the stomach, the degree of diaphragmatic impairment and the amount of increased intrathoracic pressure. The diagnosis is made by roentgen and esophagoscopic findings of a portion of stomach above the diaphragm, absence of the hiatal "pinch-cock" action and redundancy of the esophageal mucosa. The treatment is surgical, medical, mechanical or dietary. Surgical treatment is preferable if the symptoms are progressive. Relief of obstruction by dilatation and treatment of ulceration can be accomplished by endoscopic means.

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Fig. 1, Case 1.—Hiatal Relaxation with Gastro-Intestinal Symptoms.

A 38-year-old man experienced vague gastro-intestinal symptoms for 10 years. Repeated roentgen examinations were reported as normal, and the patient was labeled a psychoneurotic. Further studies revealed a relaxed esophageal hiatus. At esophagoscopy the hiatus was widely open, and the stomach was easily entered without the normal "pinch-cock" constriction.

Relaxation of the hiatus probably represents the first stage of esophageal hiatal hernia.

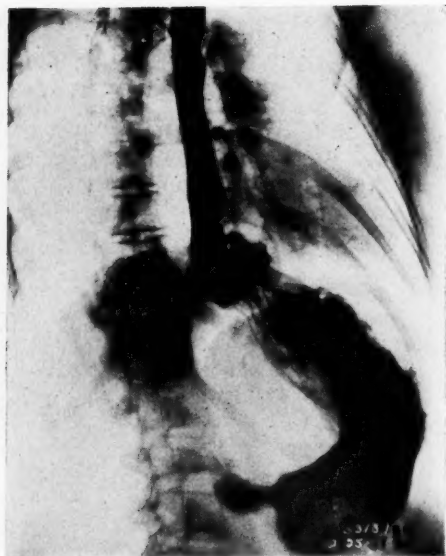


Fig. 2, Case 2.—Hiatal Hernia with Cardiac Symptoms.

A 53-year-old housewife had been complaining of a burning pain in the back and midthoracic region for two years. She had been treated for a cardiac disorder without relief. Recently when difficulty in swallowing liquids and solids occurred with a loss of 40 lbs. of weight, a roentgen study of the esophagus was performed revealing a herniation of the stomach through the hiatus.

On direct examination the entire thoracic esophagus was dilated with mucosal redundancy throughout. Gastric mucosa was encountered 31 cm. from the upper alveolar margin. The esophagogastric junction was dilated, and a considerable portion of stomach could be inspected above the diaphragm level.



Fig. 3, Case 3.—Hiatal Hernia Simulating Cholecystitis.

A 57-year-old woman had symptoms suggestive of gall bladder disease, and cholecystectomy was performed without benefit. She complained of pain in the lower right abdomen, burning sensation in the chest, regurgitation about one hour after eating and weight loss.

The roentgenogram revealed a small hiatal hernia. On esophagoscopy there was relaxation of the hiatus esophageus. No stenosis was found.





Fig. 4, Case 4.—Hiatal Hernia and Cholelithiasis.

This 57-year-old woman never experienced difficulty in swallowing. She experienced a sticking sensation and a feeling of pressure referred to the ensiform cartilage and radiating through to the back, which became aggravated on taking meats and fruit juices.

Gall stones in addition to a hiatal hernia were demonstrated on the roentgenogram. Redundancy of the upper thoracic esophagus was observed esophagoscopically. Transition from esophageal to gastric mucosa occurred 32 cm. from the upper alveolar process. There was no stenosis at this point, but the mucosa exhibited superficial erosion.



Fig. 5, Case 5.—Hiatal Hernia with Symptoms of Pharyngeal Obstruction.

A 60-year-old housewife complained of pain and lodgment of food on the left side of the throat for six years. There was no difficulty with liquids and no other symptoms.

On roentgen examination a hiatal hernia was present with about  $\frac{1}{3}$  of the stomach above the diaphragm level. There was some delay in the passage of barium through the esophageal orifice with reflux backward and dilatation above. The lumen appeared to be gaping and stiff suggesting malignancy.

Esophagoscopy disclosed considerable food and fluid in the esophagus. An area of keratosis was noted along the right lateral wall at the esophagogastric junction, and tissue removed from this area was reported as benign. Redundancy of the esophageal folds was found, and gastric mucosa was situated above the diaphragm level.



Fig. 6, Case 6.—Hiatal Hernia with Ulceration Simulating Carcinoma.

This 42-year-old man was sent to Jefferson Hospital with a diagnosis of carcinoma of the esophagus. He presented symptoms of epigastric pain, gas, belching and regurgitation of one year's duration. Roentgen examination one year previously revealed no abnormality. Recently he experienced a burning pain, usually at night, which was relieved only by vomiting. A sensation of something "stuck" behind the sternum in the region of the suprasternal notch could be relieved by drinking water, milk or hot coffee. There had been hematemesis on several occasions, and the patient had lost 10 lbs. of weight in the past month.

On roentgen examination a small ulcer crater was found at the site of constriction with intermittent spasm and slight dilatation above.

Esophagoscopy revealed a relaxation of the hiatus and superficial ulceration on the right lateral wall at the esophagogastric junction. Histologic report of the tissue removed from the ulceration was chronic inflammation.

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## LXXI

### SYPHILITIC "TUMOR" OF THE RIGHT BRONCHUS

#### CASE REPORT

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Prior to the description of the tubercle bacillus by Robert Koch in 1881, pulmonary syphilis was rather commonly diagnosed; however, since 1881, the number of cases described as "pulmonary syphilis" has declined precipitously until the present time when such cases are considered of sufficient interest to warrant a specific report in the literature. Reports of pulmonary syphilis appearing in the older and in the recent literature<sup>1-31</sup> leave no doubt as to the authenticity of this clinical entity. On the other hand reports of syphilitic gummata of the major bronchi appearing in the American literature are exceedingly scarce despite many references to bronchial syphilis which can be found in foreign literature, especially the French.

The scarcity of such reports in the American literature is difficult to explain, especially in the light of a statement made by Forbus<sup>10</sup> to the effect that in contrast to the rarity of pulmonary parenchymal syphilis is the relatively high frequency with which syphilitic infection of the larger bronchi and trachea occurs. He further goes on to describe those lesions and states that gummatous lesions of the bronchi develop in the submucosa of the walls and are most commonly found in the larynx, at the bifurcation of the trachea, and are followed by chronic ulceration which frequently involves the neighboring structures. In our particular case the lesion appeared on the medial aspect of the right bronchial wall approximately 1 cm. proximal to the level of the middle lobe orifice. It consisted of a pendulous soft tumor protruding approximately .5 to 1 cm. beyond the level of the carina, thus extending into the lower portion of the trachea. The terminal portion of the tumor appeared whitish gray and degenerative.

#### REPORT OF A CASE

J. F., aged 47, male, was seen February 19, 1945, complaining of difficult breathing.

The patient stated that he was "gassed" (mustard gas) in the last war and that following that episode he had difficulty in breathing until 1925. This difficulty was described as "severe asthma." Following 1925 the condition improved and "cleared up" but left him with a "chronic bronchitis and cough" which gradually improved, especially after he changed his residence to Reading which he did about 15 years ago. He stated, however, that about five or six months ago his "chest began to get congested again," his "nerves were upset," and that he was not as efficient at his work as he had been previously. He stated further that this condition which he described as "asthma" became progressively worse, forcing him to suspend work temporarily. He returned to work in one week but every 15 or 20 minutes "had to stop to get his breath." At this time he consulted his personal physician who studied him for sensitization phenomena. Skin tests showed three positive reactions out of a total of 30 scratch tests. (The reacting antigens could not be named.)

A routine roentgenogram of the chest revealed pulmonary markings described as suggestive of bronchopneumonia or virus pneumonia. He was admitted to the hospital at this time, February 19, 1945.

The past history was irrelevant except as it refers to the respiratory system. He gave no history of night sweats, chills, fever or loss of weight. Cough was described as productive of mucus and mucopurulent sputum but no hemoptysis or streaking was experienced prior to his first admission to the hospital on February 19, 1945. However, he did experience some streaking and raised a small quantity of blood just prior to his second admission on March 9, 1945.

A review of the several systems added no additional significant information.

Other than the fact that the patient's grandmother died of diabetes and his uncle died of pulmonary tuberculosis, there are no significant facts revealed in the family history.

The patient smokes one to one and a half packs of cigarettes daily and has done so for many years. He uses alcoholic beverages and coffee in moderation.

*Physical Examination (Essential Findings Only).*—Examination revealed a well-developed, well-nourished adult white male lying in bed (in the "semi-Fowler" position), mentally alert and appearing

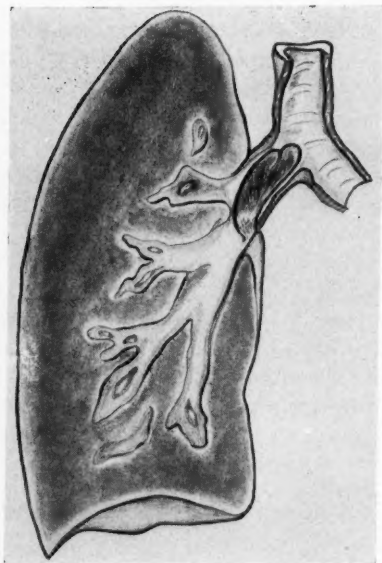


Fig. 1.—Diagrammatic representation, illustrating the position and the relationships of the tumor in the right tracheobronchial tree. Vertically the entire right bronchial tree was occluded. Only a "trickle" of air gained entrance into the upper lobe bronchus, thus permitting aeration of only a small segment of the apex.

more acutely than chronically ill. He was able to answer questions freely and intelligently. His respiratory rate appeared rapid and each respiratory effort was associated with an audible wheeze.

**Head:** The ears were normal. The pupils were regular, and reacted to light and in accommodation. The pharynx showed a slight inflammatory reaction and a prominence of the lymphatic tissue. There was a yellowish mucoid material present, apparently arising in the nasopharynx. The patient was edentulous but the mucous membranes appeared smooth and clear.

**Chest:** The first examination of the chest, made February 19, 1945, showed it to be symmetrical; expansion normal; intercostal spaces normal. Percussion note was hyperresonant over both right and left hemithoraces. Auscultation revealed breath sounds audible throughout. On inspiration there was loud inspiratory wheeze and the sounds heard on the expiratory phase were coarse and rough.



Voice sounds were normal except on the left side where the whispered voice sounds were increased both anteriorly and posteriorly.

All other physical findings were normal or unrelated except that the reflexes of the upper extremities were apparently decidedly diminished.

A second examination of the patient was made on March 9, 1945, at which time the patient was definitely acutely ill.

The eyes reacted only slightly to light and not in accommodation. The tongue was pink to red (not beefy) but not tender.

Chest: Examination of the chest showed motion almost absent on the right side, exaggerated on the left. Respirations were rapid but not labored. Tactile fremitus was absent. The percussion note was dull to flat throughout from above downward anteriorly and posteriorly on the right side, and normally tympanic on the left. On the right side breath sounds were faint to absent over the upper one fifth and absent below the plane of the second rib anteriorly. Crepitant râles were heard at the apex and in the immediate infra-clavicular area, posteriorly and anteriorly. All other sounds were absent below this level. On the left side the respirations were markedly accentuated but otherwise normal throughout. An audible respiratory wheeze, similar to that heard at the time of first admission, was a prominent feature at this time.

Neurological Examination: Marked tremor of both hands and reduced reflexes of the upper extremity.

*Laboratory Findings:*

Urine—all findings within normal limits.

*Hematology*

	2/20/45	2/23/45	3/10/45
Hemoglobin	76%	79%	98%
Red blood cells	3,930,000	3,960,000	4,300,000
White blood cells	11,450	10,800	18,450

*Differential*

Band	4%	2%	11%
Poly. Neutrophiles	63%	79%	65%
Eosinophiles	4%	2%	
Lymphocytes	25%	13%	18%
Monocytes	4%	4%	6%

Serological Reaction: Wassermann—plus 4; Kline—plus 4.

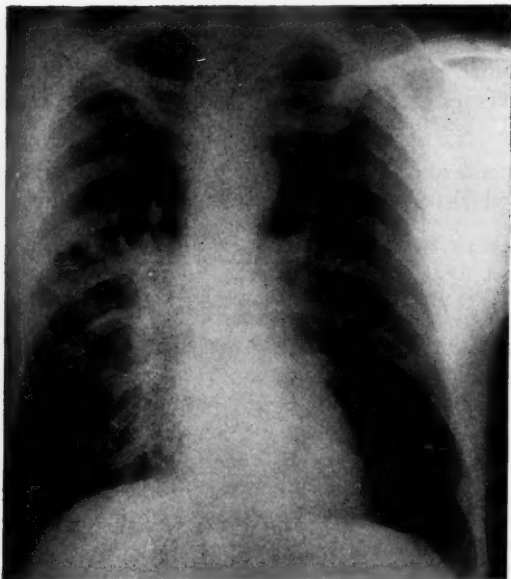


Fig. 2.—Roentgenogram. The diagnosis was primary atypical pneumonia at the time of the patient's first admission.

Roentgenograms from Judd, A. R., *Diseases of the Chest*, 1947, courtesy of the F. A. Davis Co., Philadelphia.

An electrocardiogram and fluoroscopic study showed that the heart (E.K.G.) itself was "not out of normal range." The aorta, however, showed (fluoroscopically) a degree of arteriosclerotic change with saccular enlargement of the ascending portion greater than would be considered normal.

The report of the sputum examination stated: "No acid-fast organisms and no other organisms of particular significance found."

*Operation:* A bronchoscopic examination was performed and removal of tissue from the right stem bronchus was done in two stages.

The first postoperative diagnosis was primary carcinoma of the right bronchus. The second operative diagnosis was syphilitic granuloma of the right bronchus.

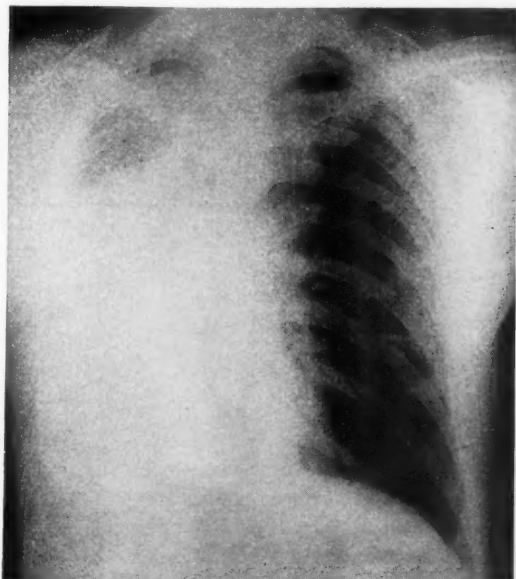


Fig. 3.—Roentgenogram made 22 days later showing extensive atelectasis of the right lung.

The interpretations of the x-ray films of the chest were concluded as follows:

Roentgenogram of the Chest (2/20/45): "We note marked density of the right hilum with a nodular infiltration in the second zone, particularly in the lower half of the lung. The apices and left lung appear to be normal. There is some thickening of the interlobar fissure on the right side" (Fig. 2).

Roentgenogram of the Chest (3/11/45): The film "showed complete obliteration of the right lung field up to the second rib anteriorly and above this level there is diffuse floccular infiltration a bit more dense than that which was noted in the lower part of the right lung when first studied. The trachea is drawn sharply to the right. The heart and mediastinum are drawn into the right chest. This is an atelectatic lesion due to bronchial obstruction" (Fig. 3).

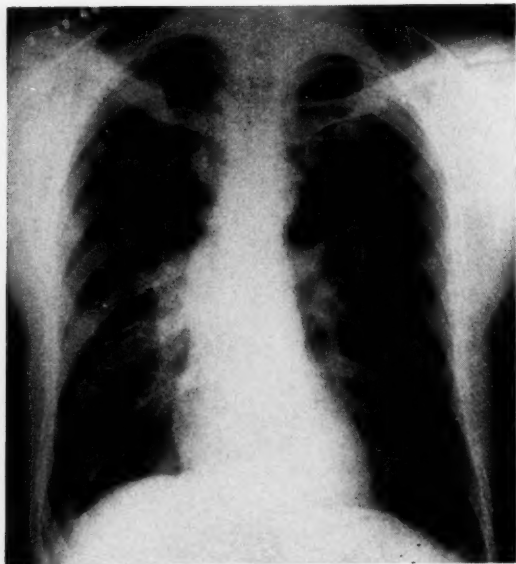


Fig. 4.—Roentgenogram showing complete resolution of process following removal of the obstructing mass from the right bronchus and administration of antiluetic therapy.

Roentgenogram of the Chest: (3/29/45): "On restudy of the chest we note approximately the same infiltration in the right hilum as was noted on first study. There has been marked absorption of the previous infiltration with renewed aeration over the right lung field and very little tracheal shift is noted" (Fig. 4).

The patient's clinical course (February 10 to February 28, 1945) was essentially uneventful. Both sulfadiazine and penicillin were administered in appropriate amounts. The temperature remained elevated throughout the period of hospitalization, reaching a peak of  $101.4^{\circ}$  F. but averaging  $99^{\circ}$  to  $100^{\circ}$  during his first admission to the hospital. In other respects, however, no unusual findings were noted except that there were persistent râles heard posteriorly throughout the right lung field and the patient complained of "some throat irritation."

After discharge the patient was attended at home and continued to run a constant temperature of  $101^{\circ}$  to  $102^{\circ}$  F., was becoming

progressively weaker and was complaining of more marked "tightness" in his chest. Rehospitalization was then advised and the patient was readmitted on March 9. An x-ray film was taken at that time.

As a consequence of the x-ray findings, (Figs. 2-4) the patient was referred for bronchoscopic examination by his attending physician.

The bronchoscopic examination revealed a mass of tissue completely filling the right main stem bronchus and extending as a rounded blunt finger-like projection into the lower trachea for about .5 cm. to 1 cm. (Fig. 1). The terminal area of the tumor was rather macerated and appeared "pale" in comparison with the remainder of the tumor mass. As much of the tumor was removed as bleeding permitted and a presumptive diagnosis of primary carcinoma of the bronchus was made.

A second endoscopy was performed seven days later and the major portion of the remaining tumor similarly removed. At the completion of the operation the bronchial tree was well aerated and the site of the origin of the tumor appeared to be on the medial aspect of the bronchus just above the level of the middle lobe orifice. At least 90 per cent of the entire tumor had been removed during the course of these two procedures.

Further removal of tumor tissue was abandoned and in view of the report of the microscopic examination antiluetic treatment was instituted and is being continued at this time.

After reaeration of the right lung the patient showed a dramatic clinical and symptomatic improvement, his temperature gradually returned to normal and he was discharged to carry on appropriate antisyphilitic treatment.

Following a period of antisyphilitic treatment the patient's care was reported taken over by one of the Naval Hospitals and further follow-up data is not available. It can be confidently reported that from the pulmonary standpoint the condition had completely resolved and full recovery realized. Cough, expectoration, and clinical manifestations were absent.

Treatment in cases of this type consists of appropriate antiluetic therapy. Scar tissue formations and consequent distortion, contracture, and narrowing of the lumen with complete bronchial obstruction are definite dangers, more especially if too energetic antisyphilitic therapy is practiced. For this reason potassium iodide

and similar agents are advisedly withheld and heavy metal therapy (bismuth or mercury) suggested. Opinions regarding the use of penicillin therapy cannot be expressed at this time because of the lack of available data.

*Diagnosis:* The first impression in this case, gained from the gross appearance of the tumor at the time of the first bronchoscopy, was, of course, primary bronchogenic carcinoma; however the histopathological examination of the tissue removed at operation, made and reported by George Des Jardins, M.D., in conjunction with a highly positive serological reaction for syphilis, disproved the first impression and established the true nature of the tumor. Further confirmation was made by Carl V. Weller<sup>30</sup> of the University of Michigan, who also examined the tissue and submitted the following opinion: "We have been unable to demonstrate spirochetes in this material, but this is not surprising in view of the infrequency with which anyone has been able to demonstrate spiral organisms in caseating gummas. Negative results in this respect do not carry much weight against the diagnosis. Histologically, this is compatible with a caseating gumma. No other organisms have been found and the clinic abstract submitted tends to support the diagnosis of lues. We have found no evidence of neoplasm."

In view of these reports and the favorable response of the patient to antiluetic treatment, a diagnosis of syphilitic tumor (gumma) of the right bronchus was considered justified.

*Comment:* As far as can be ascertained, this case represents a unique occurrence, one for which a counterpart has not been found in modern literature. Edson<sup>9</sup> reports one case of a bronchial syphilitic involvement occurring in a 36-year-old West African negro which he describes as a "bar-like granulomatous process . . . on the posterior wall occurring in conjunction with a right lower lobe pulmonary lesion." In the case herein presented, distant luetic lesions were apparently absent except as regards the aorta which appeared to show an increased arteriosclerotic change with saccular enlargement of the ascending portion. Such a description certainly suggests the possibility of an existing concomitant syphilitic aortitis. There is no other suggestion of the existence of other distinct lesions.

#### SUMMARY

A case of a syphilitic tumor (gumma) arising in the right stem bronchus is reported.

304 NORTH FOURTH STREET.

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## ADENOMA OF THE BRONCHUS

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In 1942, a series of 35 cases diagnosed as adenoma of the bronchus was reported.<sup>1</sup> Certain of the clinical features, the histological appearances, therapeutic procedures employed and end results were presented.

Briefly summarized, the end results were: five patients were treated surgically, three by lobectomy and two by pneumonectomy. There was one operative fatality. Four died from causes related directly to the tumor. Three were due to bronchopulmonary infection and in the fourth case carcinoma developed at the site of a bronchial adenoma treated five years previously. There were four deaths due to intercurrent conditions. Twenty-two patients were treated by bronchoscopic diathermy. Seven of these were free from tumor and from symptoms for 5 to 11 years. Two were tumor-free but had bronchiectasis. Thirteen still were under treatment, seven of these being symptom-free but tumor still remained and in two there was tumor present with symptoms. Three had recently come under observation and no opinion could be expressed at that time concerning the prognosis. In one case there was adenoma involving the lower end of the trachea and extending into both main bronchi.

Since this report, the patient with adenoma of the lower end of the trachea and both bronchi has died from tracheal obstruction. Three have died from intercurrent diseases. Five patients have been treated surgically, three by pneumonectomy and two by lobectomy with one death. Surgical treatment has been recommended in four additional cases because of the persistence of tumor and also of symptoms. Nine are tumor-free but two have bronchiectasis. From this follow-up report it will be observed that in a number of cases the disease progressed to a point where bronchoscopic treatment proved inadequate and surgical intervention became necessary. Nine patients remain tumor-free.

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During the past six years an additional 20 cases of adenoma have come under observation. Thirteen of these involved the right bronchus, five the left bronchus and two were found in the trachea. The cases were equally divided, 10 occurring in men and 10 in women. Eleven were between 23 and 40 years of age.

The clinical features were not unlike those observed in our previous series and in the reports of other writers. Hemoptysis was a common symptom. Since these tumors are slow growing, the common clinical and radiographic finding was bronchial obstruction with atelectasis and a varying degree of bronchopulmonary infection beyond the point of stenosis.

The treatment employed in these cases was as follows:

Bronchoscopic diathermy	10 cases
Bronchoscopic diathermy with pneumonectomy	2 cases
Bronchoscopic diathermy with lobectomy	1 case
Pneumonectomy	2 cases
Lobectomy	3 cases
Surgical treatment was necessary in the two cases of tracheal adenoma.	

In all cases where it appeared possible to remove the endobronchial tumor by diathermy, forceps removal or coring, such a procedure was carried out. The case was then restudied, a tomographic examination was made to ascertain if there was an extrabronchial tumor, and bronchographic studies were carried out to determine if there was bronchiectasis distal to the tumor. If nothing was found to indicate an extrabronchial tumor or the presence of suppuration beyond the point of obstruction, the patient continued to have bronchoscopic care. The bronchus was inspected at intervals to check on local recurrence of the tumor or stenosis due to extrabronchial changes.

If there was local recurrence, diathermy was carried out; if there was evidence of stenosis due to an extrabronchial lesion, its location and the question of interference with drainage of secretions were determined in order that a decision on whether surgical treatment was indicated could be made. In three cases there was progressive stenosis of the bronchus after the endobronchial portion of the growth had been destroyed. There was roentgen evidence of an extrabronchial mass and surgical treatment was carried out. While adenoma grows slowly and appreciable changes in bronchoscopic appearances may be observed only after long periods of observation, if there is progressive stenosis due to an extrabron-

chial tumor surgical extirpation should not be delayed unnecessarily. In one case, delay in performing a lobectomy for adenoma of the left lower lobe bronchus ultimately necessitated pneumonectomy because of progressive encroachment of the tumor on the orifice of the left upper lobar orifice. The occurrence and persistence of pulmonary suppuration due to obstruction that cannot be relieved temporarily, as is the case in an endobronchial adenoma, also increase the difficulties and hazards of surgical treatment.

Certain patients are not considered suitable for bronchoscopic treatment and for these surgical treatment is indicated when the diagnosis is made. These usually have tumors in the upper lobar bronchi which are inaccessible to bronchoscopic manipulation. In addition, the vascular type of tumor that bleeds freely whenever any bronchoscopic manipulation is carried out also is more safely treated by surgery. There were three upper lobe tumors which required surgical treatment. In each a portion of tumor projected into the main bronchus so that an adequate biopsy specimen could be secured but appropriate endobronchial treatment was not possible. In one of these there also was encroachment on the main bronchus immediately distal to the upper lobe orifice. This tumor also was very vascular and hemoptysis was a frequent symptom.

In two cases of bronchiectasis with pulmonary fibrosis lobectomy was performed. While an occasional patient with bronchiectasis may become practically symptom-free after removal of an endobronchial adenoma, lobectomy seems the procedure of choice unless there are contraindications.

Since bronchial adenoma is a very slow growing type of tumor, it is difficult to arrive at final conclusions until one has had an opportunity to observe patients for a considerable time. It is important, therefore, to keep a careful check on them to determine not only if there is local recurrence but also if there is evidence of extrabronchial growth with the production of stenosis. Body section roentgenography has been of great assistance in this respect.

Bronchoscopic treatment should be carried out in all cases in which there is a reasonable chance to remove with forceps or destroy by diathermy all of the endobronchial portions of tumor. While no definite limitations can be placed on the number of treatments, one should accomplish one's objective in three or four attempts. The anatomical appearance of the tumor will aid in determining if it can be destroyed. A pedunculated tumor can be more readily and promptly removed or destroyed than a sessile mass.

An associated long-standing bronchiectasis with pulmonary fibrosis should influence one's decision. Bronchoscopy is of value in establishing and maintaining drainage and ventilation of the lung distal to the obstruction preparatory to surgical treatment.

In our earlier series the opinion was expressed that bronchoscopic treatment would be adequate in a majority of these cases. Subsequent developments have indicated that patients previously considered as symptom-free later developed bronchial obstruction due, not to recurrence of tumor within the bronchus, but to changes either within the bronchial wall or extrabronchially which produced bronchial obstruction that could not be relieved bronchoscopically and ultimately terminated in chronic pulmonary sup-puration.

The surgical indications vary with the opinions of various writers. Some recommend surgical removal of all adenomas on the assumption that many become malignant. Medical literature does not support this thesis. Experience has shown that a certain number of benign slow-growing epithelial tumors may assume malignant characters. The occurrence of malignancy in cases of adenoma of the bronchus has been relatively infrequent. Surgical treatment is indicated in tumors inaccessible to bronchoscopy, in cases in which one cannot establish and maintain an adequate airway whether or not there is evidence of extrabronchial tumor, hemorrhage, and bronchiectasis with pulmonary fibrosis beyond the site of the tumor.

Tracheal tumors present an entirely different problem. There have been three in the entire series. One, previously reported as a tumor of the lower end of the trachea involving both bronchi, terminated fatally by asphyxiation and terminal pneumonia. Two additional patients have come under observation; one, a woman who had an adenoma of the thoracic portion of the trachea, and the other, a man, who had an adenoma of the cervical portion of the trachea. These will be reported in detail:

CASE 1.—Woman, aged 27 years, developed shortness of breath six years before admission to the Clinic. She had been treated for asthma for two years and later a growth was discovered by bronchoscopy. This was ultimately diagnosed as adenoma and irradiation therapy was given without benefit. Subsequent attempts were made to remove the growth by forceps and diathermy with little success. When she was admitted to the Clinic in 1946, there was marked stenosis of the thoracic portion of the trachea but there was

no ulceration. Many small masses were removed with forceps or treated by diathermy but the tracheal lumen became progressively smaller and surgical treatment was carried out. Dr. J. H. Gibbon, Jr., did a thoracotomy and found a large tumor involving the left lateral wall of the trachea. In attempting to remove it he also removed a portion of the tracheal wall, leaving a large defect in the airway. The defect was repaired and the patient appeared relieved for a time but succumbed 18 months later from tracheal obstruction.

CASE 2.—Man, aged 54 years, gave a history of cough for eight years with recent hemoptysis. By mirror laryngoscopy there was observed a tumor in the trachea about 1 cm. below the level of the vocal cords. A roentgen study showed encroachment by a soft tissue mass on the tracheal air column. Direct examination revealed a rounded, firm, smooth mass attached to the right side of the trachea and obliterating about two-thirds of the tracheal lumen. There was superficial ulceration on its inner aspect. Biopsy revealed an adenoma.

Tracheostomy was performed; tracheal rings 2 to 6 were incised slightly to the right of the midline in close relation to the growth. The incision was carried laterally below and above the growth, then posteriorly to the end of the tracheal rings. The growth appeared to be intimately attached to the rings and extended into the interannular spaces so that it was not possible to separate either tracheal rings or soft tissues. Following removal of the growth there was present a defect in the tracheal wall about the size of a 25-cent piece. A tracheal cannula was inserted slightly to the left of the midline below the level of the defect and the surrounding soft tissues were sutured over the tracheal defect. The patient made a prompt recovery, was decannulated and there has been no recurrence of growth nor serious stenosis of the trachea since operation 16 months ago.

#### CONCLUSIONS

1. Although bronchial adenoma may be a potentially malignant tumor this has been observed only once in our series of 55 cases.
2. The plan of treatment should be based on the bronchoscopic findings and roentgen studies, notably body section roentgenography and bronchography. If the findings indicate that the tumor is endobronchial, if there is an absence of bronchiectasis and if removal of the tumor is possible by bronchoscopic means, this probably will suffice. A periodic bronchoscopic examination should be made.

3. In the presence of certain indications, as noted, surgical treatment is indicated.

1530 LOCUST STREET.

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## THE REPAIR OF LARGE DEFECTS OF THE TRACHEA

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In July 1946 a 10-year-old boy was seen who two years previously had suffered an avulsion of the cervical trachea when struck by an automobile. The handle of the car door was thought to have passed through the anterior portion of the neck, removing the trachea from the lower border of the larynx to the suprasternal notch and tearing an opening into the esophagus. Other important structures of the neck were uninjured. As an emergency procedure the lower end of the trachea had been brought out in the suprasternal notch to serve as a tracheotomy and the lacerations of the esophagus and skin had been repaired. As our examinations showed an essentially undamaged larynx with good movement of the left vocal cord and questionable movement of the right cord, it seemed that it should be possible by some means to reconstruct the 2.5 to 3 cm. defect of the trachea and restore a normal airway and adequate phonation.

On reference to the literature little information was found regarding the reconstruction of full thickness circumferential defects of the trachea. Most of the investigative and clinical reports along this line have been concerned with the repair of tracheal or laryngeal stenosis where there has been destruction of the mucosa and constriction of the lumen but where the cartilaginous supporting framework has been intact; or with the closure of tracheal or bronchial defects following pneumonectomy or excision of small, non-circumferential full thickness segments of the tracheal wall.

LeJeune and Owens<sup>1</sup> in 1935 reported their treatment of two patients with laryngeal and upper tracheal stenosis. They recommend opening the stenosed area in the anterior midline, excising all of the scar tissue, and immediately grafting the area with a split thickness skin graft. The midline opening and the tracheotomy wound are subsequently closed after the graft is well healed. In 1945 Erich<sup>2</sup> reported a three-stage procedure which had been used in the repair of similar lesions. At the first stage the trachea and

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larynx are opened in the midline, the scar tissue is excised, and a split thickness skin graft on a sponge rubber mold is anchored in place. The midline incision is then closed. Ten days later at the second stage the sponge is removed and an acrylic obturator is fashioned to fit against the tracheotomy tube and extend through the grafted lumen to prevent subsequent contraction. The obturator, which is well tolerated by the patient, is worn for six months. The third stage consists of a plastic closure, usually by shifting local skin flaps, of the rather large tracheotomy opening which is required. Other reports such as the one of Cummings<sup>3</sup> in 1940 indicate that satisfactory results have been obtained by the mere incision of the stenotic area from within the trachea followed by the prolonged use of an obturator.

In the light of recent investigations concerning the rapid regeneration of the tracheal mucosa, the possibility is suggested that the good results from open operation and skin grafting are derived chiefly from the careful and complete dissection of the scar tissue and the prolonged use of the obturator rather than from the presence of the skin graft. It has been clearly shown<sup>4</sup> that such grafts do not undergo metaplasia but retain the characteristics of the skin from which they were taken. Previous reports of such intralaryngeal grafts assuming the gross characteristics of mucous membrane possibly indicate that the original skin graft failed to survive and that regenerative mucosa so rapidly covered the denuded area that the interpretation of results was mistaken. Further study of these questions seems indicated.

The closure of openings in the trachea or the bronchi has been of considerable interest to the thoracic surgeon, particularly in regard to suitable methods of closing the cut end of the bronchus following pneumonectomy. Although clinically various types of direct suture methods are still generally employed for this purpose, certain methods that have been developed experimentally are of interest. Rienhoff<sup>5</sup> obtained satisfactory closure of the bronchial stump in experimental animals by merely suturing pleura over the end of the bronchus. Taffel<sup>6</sup> has obtained similar results using fascia. He also obtained satisfactory healing of small full thickness defects of the cervical and thoracic trachea by covering these areas with fascia. Taffel stated that such fascial grafts did not remain viable but that they served as a temporary, air-tight scaffold which was quickly invaded and replaced by wandering cells and proliferating fibroblasts. The latter in turn became differentiated into collagen-bearing adult connective tissue which remained as a permanent sup-



Fig. 1.—Patient on admission with well-healed tracheotomy wound in the suprasternal notch. Trachea absent as far as the lower border of larynx.

porting structure spanning the defect. Regeneration of respiratory mucosa over the defect was usually complete by the second week. The cells, at first cuboidal and sparsely ciliated, quickly assumed a pseudostratified appearance and acquired their normal complement of cilia and goblet cells.

Similar results from the use of such fascial grafts have recently been reported by Daniel,<sup>7</sup> who also observed the healing of tracheal defects when they were covered with "fibrin film." Although the immediate healing of such areas was satisfactory, a moderate stricture of the trachea resulted from the contraction of the excised area. Hanlon<sup>8</sup> has recently obtained satisfactory healing of one centimeter-square defects in the tracheas of dogs when the openings were covered with patches of gelfoam. There was no evidence of stenosis at the site of the defect in animals sacrificed two months after operation.

The remarkable case reported by Scott,<sup>9</sup> of a successful primary end-to-end suture of the cervical trachea and esophagus following complete transverse division of these structures, adequately demonstrates that in spite of the marked retraction of the cut ends of the trachea following complete division, primary healing is possible if the ends can be approximated. Nach and Rothman<sup>10</sup> state that

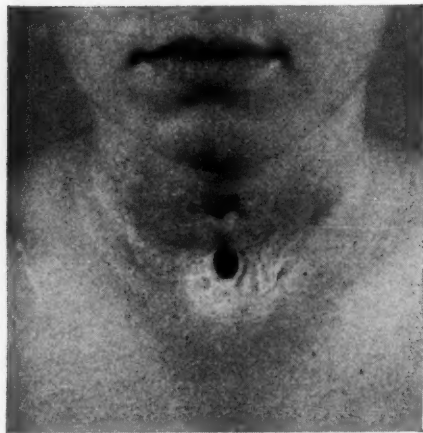


Fig. 2.—External opening made into inferior end of larynx.

primary suture in case of complete transverse division of the trachea may be performed if the ends are separated no more than 2 to 4 cm. Beyond this a breakdown of the suture line may be expected. It would seem that the distance of retraction of the divided ends would make little difference if none of the tracheal wall were actually missing as it would be assumed that the ends could be approximated under normal tension. The length of trachea that can be excised or removed and have the ends unite by primary suture has, as far as we know, not been determined. In our patient an attempt was made to mobilize and advance the distal end of the trachea so that it might be sutured to the lower border of the larynx. This, however, was found to be impossible. Contraction of the trachea after mobilization was so great that it was with difficulty that the end could again be brought up to the level of the skin.

During the time this patient was under treatment we learned of the observations of Daniel on the regeneration of the trachea and bronchi in dogs. He found in circumferential defects of the trachea or bronchi which were temporarily bridged with a metal or glass tube a substitute tracheal or bronchial wall regenerated around the tube. This regenerated wall was lined by flattened epithelial cells, and in certain of the animals well-developed cartilaginous rings were formed in the surrounding connective tissue. The rings of

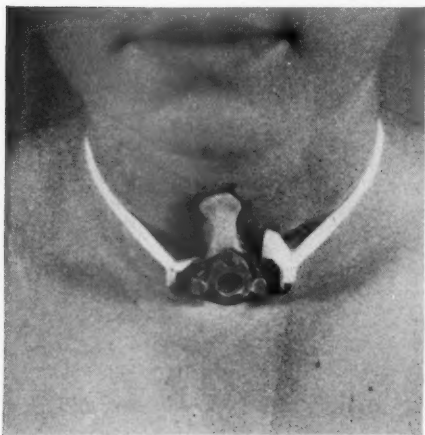


Fig. 3.—Acrylic tube in place between tracheotomy tube and larynx. Closure of tracheotomy tube permits passage of air through acrylic tube into larynx.

cartilage seemed to develop from the fibroblasts which invaded the newly formed granulation tissue. They were not outgrowths of pre-existing cartilage. The first evidence of cartilage in the defects was seen in specimens examined three weeks after operation but its subsequent growth was slow. In one animal the tube was removed from the trachea eight months after operation. Four months later the animal, which was in good health, was sacrificed. Flattened epithelial cells completely covered the defect. There were well-developed, evenly spaced cartilaginous rings present throughout the defect. The diameter of the trachea was a little more than half that of the normal trachea. This remarkable demonstration of the regeneration of a substitute tracheal wall in experimental animals suggested a method which might be used in our patient to re-establish an adequate airway.

#### REPORT OF A CASE

T. A., a ten-year-old white boy, was admitted to the Johns Hopkins Hospital on July 12, 1946. Two years previously his cervical trachea had been avulsed as has been described. There was a well healed tracheotomy wound in the suprasternal notch. The larynx on external palpation was normal, movable, and in the

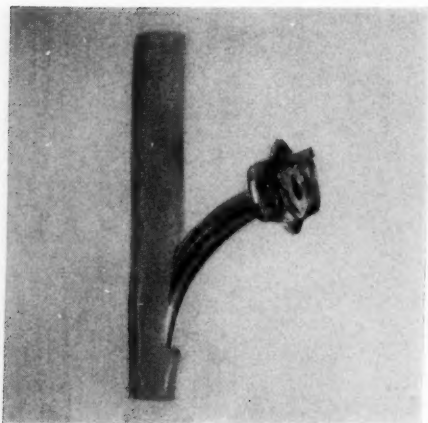


Fig. 4.—Tracheotomy tube with lucite tube which is implanted subcutaneous between the end of the trachea and the larynx.

midline (Fig. 1). Dr. Donald Proctor reported that laryngoscopic examination showed the epiglottis and the arytenoids to be normal. The left arytenoid was seen to move. The false cords and the true cords appeared normal although both were in a position of adduction most of the time. The lumen extended about 1 cm. below the cords and ended blindly in a small pocket.

At the first operation an opening was made from the lower end of the larynx to the outside (Fig. 2). An acrylic tube was prepared by Dr. Pyott of the Dental Department; this fitted over an opening in the tracheotomy tube and projected into the opening in the larynx (Fig. 3). When the tracheotomy tube was occluded air could be forced through the larynx. After several weeks of practice the patient developed a moderately good voice which although hoarse was adequate for normal conversation. At the second operation an unsuccessful attempt was made, as has been mentioned, to mobilize and advance the distal end of the trachea to the lower border of the larynx. The child was then discharged with the acrylic prosthesis in place.

He returned to the hospital on August 1, 1947, at which time it was our plan to connect the openings in the larynx and trachea with a rigid skin-lined tube fashioned from a skin flap containing



Fig. 5.—Patient with subcutaneous lucite tube in place. External opening into larynx closed.

a heavy tantalum mesh. However, at this time the experimental observations of Daniel on tracheal regeneration were called to our attention and it was decided that the method should be tried. A lucite tube was constructed that would fit over the tracheotomy tube and extend subcutaneously from inside the trachea below into the larynx above (Fig. 4). An additional opening was made in the superior surface of the tracheotomy tube so that air might pass up through the lucite tube. This was inserted and the external laryngeal opening was closed on August 15. Within a few days the patient was able to speak by occluding the tracheotomy tube opening (Fig. 5).

He was last examined four and a half months after the insertion of the tube. There was a very slight discharge present. His voice was good. The tube was surrounded by dense semirigid tissue. That portion of the lumen of the segment which could be inspected through the tracheotomy opening appeared to be lined with epithelium. No specimens for biopsy were taken. The patient was instructed to return in three months for removal of the lucite tube as it was felt that additional time should be allowed to permit the substitute tracheal wall to become as rigid as possible in order to prevent subsequent contraction.



## DISCUSSION

Of the various methods of tracheal repair that have been reported in the past, the only procedure which would seem to be of value in the reconstruction of large, full thickness, circumferential defects is that suggested by the remarkable regenerative powers of the trachea which have been observed in experimental animals by Daniel. The length of trachea that can be removed and still permit an end-to-end suture by stretching the remaining portions has not been determined. A separation of the divided ends by 4 cm. has been suggested by Nach and Rothman as a maximum for end-to-end suture. Repair of small noncircumferential defects by the use of fascia, pleura, or gelfoam all appear to have given satisfactory experimental results, but these methods would not seem applicable in the repair of the larger defects. Experiments which are now in progress in our laboratory indicate that it may be possible to repair circumferential defects by the use of tracheal homografts.

In the case presented it appears that a satisfactory substitute tracheal wall has regenerated about a subcutaneously placed lucite tube. Although the subsequent course of such regenerated segments has been satisfactory in experimental animals, it remains to be seen how such a structure will function over a long period of time in the human being.

## SUMMARY

In a review of the literature only one recently described experimental method has been found by which it would seem possible to repair large circumferential defects of the trachea. This method permits a substitute tracheal wall to regenerate about an inert tube which temporarily serves to bridge the defect. A case is reported in which this method is being used.

On July 3, 1948, 10½ months after the subcutaneous insertion of the acrylic tube it was removed. The unsupported channel, however, was not rigid enough to provide an unobstructed air way during inspiration. The acrylic tube was reinserted and is to remain in place for another six months before its removal will be attempted again.

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## LXXIV

### BRONCHOPULMONARY INFECTIONS IN ALLERGIC INDIVIDUALS

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In order to avoid misunderstanding I shall attempt to define what I mean by allergic individuals. I refer to those individuals who, because of a hereditary predisposition, react excessively to irritation, be it bacterial, chemical, mechanical, thermal, or protein. To be more specific, the mucous membranes of these individuals develop excessive edema and large amounts of exudate in response to stimuli which would not provoke these reactions in *nonallergic* persons. The pathological state is often, but not always, due to interaction of antigen and antibody. Functional disturbances of the autonomic nervous system may produce similar symptoms. Whatever the mechanism, there is strong hereditary predisposition and most of these individuals have a hyperirritable nervous system. My ideas approximate those of Lowell<sup>1</sup> who says: "In a broader sense the word allergy denotes in addition a variety of hypersensitive states arising in infections or as a result of exposure to drugs, antibiotics and the numerous preparations of plant or animal origin used in the modern practice of medicine." I suspect that Osler had allergy in mind when he said: "It is more important to know what man has the disease than what disease the man has." We are not all born with the same capacity to be sensitized to bacterial or other proteins.

I have implied that the tendency to develop this increased reaction-capacity is hereditary, and for this reason a reliable history of allergic symptoms in the family is important.

In order to evaluate the frequency and the significance of the allergic constitution in patients coming to a bronchoscopist I have studied the hospital charts of 100 nearly consecutive patients who had bronchoscopic examinations during 1947. A few charts were rejected because they were incomplete.

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Read before the Meeting of the American Broncho-Esophagological Association, Atlantic City, N. J., April 8, 1948.

TABLE 1.

DIAGNOSIS	NO. OF CASES
Bronchiectasis	20
Chronic bronchitis	15
Asthma and chronic bronchitis	10
Allergic pulmonary consolidation	4

In order to classify those who had or were capable of developing this increased reaction-capacity which we term allergy, the following criteria were tabulated:

1. Family history of allergic symptoms (asthma, hay fever, eczema, and hives)
2. Personal history of allergic symptoms (asthma, hay fever, eczema, and hives)
3. Blood eosinophilia of 5% or more
4. Eosinophils in bronchial exudate (10% or more)
5. Nasal polyps

It was found that 49 of the 100 patients studied had one or more of these criteria, which placed them in the allergic group. Table 1 gives the diagnoses of these 49 cases.

*Bronchiectasis.*—In addition to the 20 bronchiectatic patients in the allergic group, there were 6 other not demonstrably allergic patients who had bronchiectasis. Thus, out of 26 patients who had bronchiectasis, 76 per cent had evidence of allergy. Thomas and his associates<sup>2</sup> found allergy to be an etiologic or complicating factor in 73 per cent of 75 well studied bronchiectatic patients. There must be some explanation for this high incidence.

In 1944 I<sup>3</sup> suggested that the excessive mucosal edema so characteristic of allergic subjects was the factor causing atelectasis which led to bronchiectasis. I refer to edema present at the time of the severe acute broncho-pulmonary infection which initiated the bronchiectasis. Fig. 1 indicates how markedly pulmonary drainage can be impaired by mucosal edema.

Another explanation why bronchiectasis develops frequently in allergic individuals came to my mind when reading Kline's<sup>4</sup> description of tissue necrosis due to severe allergic reaction. Most bronchiectatic patients date their cough from a severe acute bronchopul-

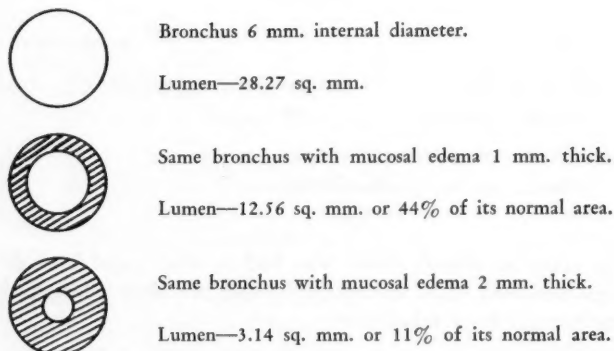


Fig. 1.—Diagram indicating how much even a 6 mm. bronchus is obstructed by mucosal edema 2 mm. in thickness.

monary infection in childhood. Autopsy specimens described by Lisa and Rosenblatt<sup>5</sup> showed a pathologic state which could be due to a necrotizing allergic reaction to bacterial proteins. They state: "Widening of the bronchi in bronchiectatic disease is the direct result of necrotic inflammation of the bronchial wall and the adjacent parenchymal tissue." The necrotizing effect of bacterial sensitization is implied in the following sentence by Cooke:<sup>6</sup> "The tuberculin skin test is an indication of this allergy to tuberculoprotein which, *purely as a result of the sensitization of the host*, has become an active necrotizing poison."

We will have fewer cases of bronchiectasis if acute bronchopulmonary infections are adequately and promptly treated by large parenteral doses of penicillin and by bronchoscopic aspiration, when roentgen examination shows "unresolved pneumonia" due, in reality, to bronchial obstruction by edema and gummy exudate.

Turnbull<sup>7</sup> has, I think, correctly shown how recognition and treatment of food sensitivities can reduce the mucosal edema which is a factor prolonging "unresolved pneumonia" in some cases.

There are other reasons for recognizing an allergic factor in bronchiectatic patients. Mucosal edema, hypersecretion, and bronchospasm due to coincident food or inhalant sensitivity can be reduced by eliminating allergens to which the patient is found sensitive. Hyposensitizing injections of autogenous vaccine prepared

from endobronchial exudate are also helpful for those patients not suitable for lobectomy.

There are still other reasons for recognizing the allergic constitution. Characteristic of infections in allergic people are rapid onset, violent course, and slow regression. Prompt treatment will prevent irreversible damage.

In treatment one should, in addition to penicillin, use antihistaminic drugs, sympathomimetic drugs, and aminophylline to decrease the mucosal edema and the bronchospasm which is so often present.

*Chronic Bronchitis.*—Fifteen patients in the allergic group had chronic bronchitis. In contrast, only 2 in the nonallergic group had chronic bronchitis. This proportion suggests that allergy was a factor responsible for the chronicity.

Cultures of exudate obtained by bronchoscopic aspiration were made on blood agar plates containing penicillin .05, .2, and .5 units per cc. If sensitive organisms were found, the patient was treated with penicillin, using 50,000 to 100,000 units intramuscularly or subcutaneously, every 3 hours, day and night, for 7 to 10 days. By this method, some long-standing cases were permanently cured. Streptomycin-treated blood agar plates are also used to determine whether or not this drug should be used in preference to, or in addition to, penicillin. I do not use sulfadiazine for these infections because it is inferior to penicillin and because it frequently sensitizes allergic individuals.

Skin tests were made in most cases to discover extrinsic allergens. Food sensitivity could occasionally be detected by keeping a food and symptom diary, or by trial diet, but these methods are very difficult to evaluate unless the infection is first eradicated, or greatly reduced, by penicillin therapy.

The following case report illustrates some of the points in diagnosis and treatment.

L. T., female, aged 36, gave a history of chronic productive cough of 22 years' duration, which had become much worse during the last two years. Recently she expectorated two or three ounces of sputum daily. She had pneumonia frequently during childhood. Seven years ago a diagnosis of bronchiectasis was made, but bronchography showed normal bronchi and roentgen examination showed no abnormality. Cultures made from a bronchoscopic specimen showed streptococcus viridans and staphylococcus aureus, both sensitive to penicillin in concentration of .2 unit per cc. Smears showed many eosinophils in the bronchial exudate. She received penicillin, 50,000 units intramuscularly every three hours, day and night, for seven days. Following this therapy, her cough and expectoration decreased greatly. Wheat, beef, and white potatoes were eliminated from her

diet because she showed strongly positive reactions to skin tests of these foods. Her pillows and mattress were covered with dustproof covers because she had a positive skin test to feathers. One month later she was absolutely free of the chronic cough which had been present for 22 years.

Some of these allergic patients with chronic suppurative bronchitis were thought to have bronchiectasis because they had large amounts of sputum. The latter can be ruled out only by bronchography.

Several patients in this group had what Watson and Kibler<sup>8</sup> call basal allergic bronchitis, which closely simulates bronchiectasis. Bronchography is required for differential diagnosis.

Autogenous vaccine therapy was used for those patients who had infection due to organisms not sensitive to penicillin, or when a moderate amount of cough persisted after penicillin therapy.

It clarifies the problem in my mind to think the symptoms are due to local infection and sensitization of the bronchial mucosa by bacterial protein.

The question might well be asked when we advise vaccine therapy, are we immunizing or hyposensitizing? I think the latter concept should be emphasized because it focuses our attention on the need for using extremely small doses of vaccine. We are all well aware of the harmful effects of excessive doses of pollen antigens, but not so aware of the ill effects of excessive doses of bacterial antigens. No one would think of using large doses of tuberculin, and yet frequently we see patients who have been made worse by large doses of bacterial vaccine. Cooke<sup>6</sup> resolves the difference in terminology as follows: "Hyposensitization was once suggested by me to designate clinically lessened sensitiveness. It is correct if used for the clinical state only, but with present knowledge it seems preferable to speak of lessened reactivity as immunity, relative or partial to be sure, but still an immune state." Clerf,<sup>9</sup> Van Loon,<sup>10</sup> and Crump<sup>11</sup> have also emphasized the value of vaccine therapy. Solis-Cohen<sup>12</sup> states: "Successful vaccine therapy requires skillful administration," and gives what I think are reliable rules for selecting the appropriate dose.

*Asthma and Chronic Bronchitis.*—These patients were similar to those of the preceding sub-group, but in addition had intermittently the type of dyspnea and wheezing characteristic of bronchial asthma. For this type of disease Cooke<sup>6</sup> uses the term "infective asthma." The symptoms are due to mucosal edema, thick exudate, and bronchospasm. In certain cases one of these factors may pre-



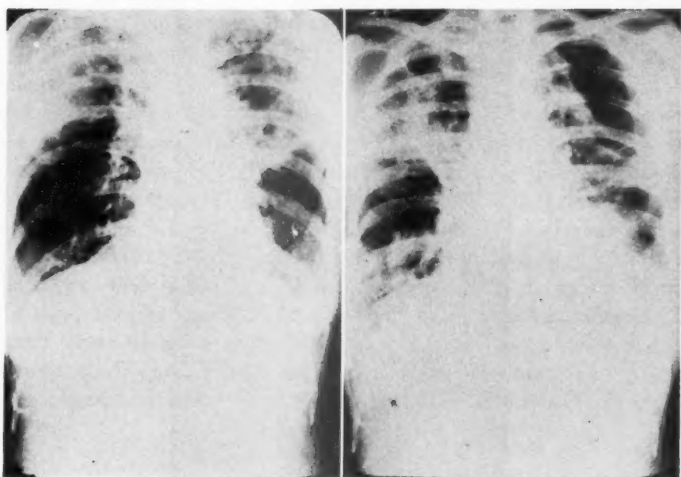


Fig. 2.—Loeffler's syndrome simulating tuberculosis; film made November 1, 1935.

Fig. 3.—Artificial pneumothorax increased the dyspnea; film made December 10, 1935.

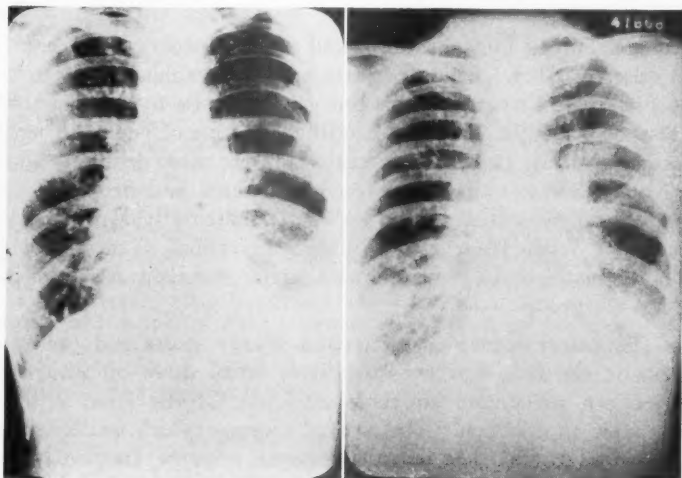


Fig. 4.—The dyspnea was completely relieved by one bronchoscopic aspiration on February 1, 1936. Film made February 18, 1936.

Fig. 5.—Film made May 5, 1936. The exudate this time is seen chiefly in both lower lobes.

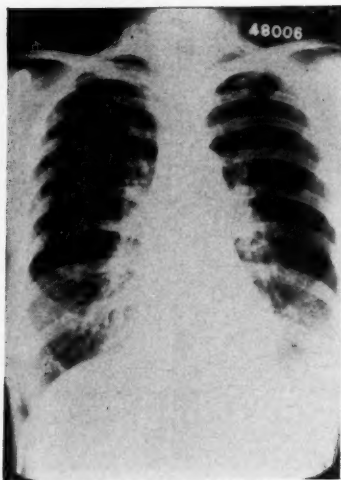


Fig. 6.—Film for May 16, 1936, following two bronchoscopic aspirations which completely relieved the dyspnea. The patient gained 30 pounds in weight during the next six months.

dominate, but all must be considered when planning treatment for symptomatic relief. Those patients having bronchial infection due to penicillin-sensitive organisms had good response to large parenteral doses of penicillin. I have discontinued the use of penicillin aerosol treatment because two asthmatic patients were made definitely worse. My conclusion was that the bronchial mucosa had become locally sensitized to penicillin. Some asthmatic patients had prompt and spectacular relief from bronchoscopic aspiration, as described by Lell.<sup>13</sup> Treatment of nonbacterial allergies was used as in the preceding sub-group.

The best evidence that bacterial allergy exists and can cause asthma is the fact that even relatively small doses of autogenous vaccine can precipitate an acute asthmatic attack from 2 to 24 hours after an injection. The delayed response which usually occurs is analogous to the delayed inflammatory response frequently seen following intradermal injection of a vaccine.

Penicillin therapy may be thought of as a means of eliminating an allergen because it aids in destroying the organisms in the bronchial mucosa.

*Allergic Pulmonary Consolidation.*—This diagnosis used by Hansen-Pruss and Goodman<sup>14</sup> is, I think, useful to describe pulmonary densities sometimes shown by x-ray examination in allergic patients. They state: "We believe that allergic pulmonary consolidation is an expression of sensitization to nonspecific bacteria and that it can occur in constitutionally allergic individuals as well as in individuals who acquire the allergic response." These radiopaque areas may be large or small and have any distribution. Loeffler's syndrome comes under this classification, but not all such patients have severe asthma. These densities are easily confused with tuberculosis, or their bizarre shape may prompt such diagnoses as virus infection, fungus infection, sarcoid, or unresolved pneumonia. The patchy areas of atelectasis so common in allergic persons are frequently misdiagnosed as tuberculosis. Repeated smears to rule out tuberculosis and smears showing many eosinophils will clarify the diagnosis.

Each of the four patients in this group had prompt symptomatic relief following bronchoscopic aspiration. Herbut and Kinsey<sup>15</sup> conclude from experimental work that Loeffler's syndrome is an allergic inflammation of the lungs and that one route by which the allergen invades is that of inhalation.

The following case report illustrates the type of disease described by Loeffler. I include it because it is the best example I have seen.

A. B., female, aged 51, had asthma since 1934. Fig. 2 shows the roentgenogram of her chest made November 1, 1935. Because the film was considered typical of tuberculosis, pneumothorax was induced at a sanatorium, even though tubercle bacilli could not be demonstrated in the sputum. The asthma promptly became worse. Fig. 3 shows the roentgenogram made December 10, 1935. Bronchoscopic aspiration on February 1, 1936, promptly and completely relieved the asthma. Fig. 4 shows the roentgenogram for February 18, 1936. Three months later, asthma recurred and x-ray examination on May 5, 1936, showed the picture illustrated by Fig. 5. The blood eosinophil count at this time was 27%. Following two bronchoscopic aspirations the asthma was completely relieved and the roentgenogram for May 16, 1936, is shown by Fig. 6. This patient has since remained well except for slight temporary asthma when she has a cold. Since bronchoscopic aspiration on two occasions so promptly cleared the densities shown by x-ray study, it is my opinion that they were due to patchy areas of atelectasis, the result of thick, gummy exudate.

#### SUMMARY AND CONCLUSIONS

1. About half of the patients referred for bronchoscopy have the allergic constitution which is partly responsible for their disease.
2. To recognize and understand this factor, the bronchologist must have some knowledge of allergy.

3. Such knowledge will aid in planning adequate therapy.
4. Bronchoscopic aspiration benefits patients with Loeffler's syndrome and other types of allergic pulmonary consolidation.
5. Allergic management helps some patients who have bronchiectasis.
6. Chronic bronchitis occurs chiefly in hypersensitive individuals.
7. Autogenous vaccine therapy is useful in treating many types of chronic bronchopulmonary infection in allergic persons, but extremely small doses should be used.
8. Examination for eosinophils in bronchoscopic specimens should be a routine procedure in patients having a chronic cough.
9. The availability of penicillin has not decreased our need for a knowledge of immunology, including allergy.
10. In vitro tests for sensitivity of organisms to penicillin and streptomycin are practical and useful.

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ENDOSCOPIC ASPECTS OF BRONCHIAL SCLEROMA  
(RHINOSCLEROMA)

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The first case to be reported is of a patient, 20 years old, suffering from rhinoscleroma and having a tracheal cannula to assure breathing, who became dyspneic and started bleeding through the tracheal fistula. The explanation for this was very unsatisfactory until bronchoscopic examination showed the trachea to be considerably narrowed and the mucosa thickened. When the lowest part of the trachea was reached, I observed some small, isolated, reddish, bleeding tumors obstructing the lumen. These tumors were removed as quickly as possible because the condition of the patient was very critical. On further examination I was able to see other tumors at the carina and at the entrance of both bronchi. The removal of all of these brought the patient back to life. Histologic examination revealed rhinoscleroma. This patient survived a few more years during which time I had to remove similar obstructive tumors that appeared periodically. Other histological examinations confirmed the diagnosis of rhinoscleroma.

Later, a similar case was observed. I was called urgently to the General Hospital to attend a patient having acute dyspnea. When I arrived the patient was dead. I proceeded immediately to do an endoscopy, and found the lower part of the trachea and the lumen of both bronchi full of small tumors having the same characteristics as those of the preceding case. All efforts to bring the patient back to life were useless. The tumors were sent to the Department of Pathology where the pathologic diagnosis of rhinoscleroma was made.

These two cases made me consider the necessity of examining endoscopically most of the patients in whom typical rhinoscleroma was present.

The results of these examinations led me to examine all persons who presented similar obstructive lesions. Many times I was able to observe unsuspected lesions of the larynx and in a small number of cases the trachea and bronchi presented similar lesions. A deep infiltration of the tracheal mucous membrane was observed as well

as characteristic nodules such as those previously described. These varied in number in each case.

I should like to present a brief description of two more interesting cases of this disease: M. A., Mexican, 30 years old, a well-nourished male, had, according to the clinical history and histopathological studies, a deformity of the nose and soft palate and stenosis of the larynx due to rhinoscleroma. Syphilis and tuberculosis studies were negative. Electrocoagulation applied to the nostrils and radiotherapy to the nose and larynx, following tracheotomy, was the initial treatment. Six months later laryngostomy was performed, after which healing was satisfactory and the tracheal cannula was removed. Following a plastic operation, the patient was discharged from the hospital. For one year the patient remained comfortable. Suddenly, dyspnea recurred and he again returned to the hospital. On tracheoscopy, a slight retraction of the scar of the old operation was seen on each side. One pedunculated, reddish, bleeding tumor mass which partially obstructed the airway was removed, and the symptoms were immediately relieved. The pathologist confirmed the nature of the lesion (rhinoscleroma). In spite of further radiotherapy, subsequent endoscopies showed recurrence. Since then, four years ago, the patient has been treated by dilatation with Schroetter dilators through the mouth, with apparent success. The voice has improved and he has been able to resume his former occupation as a railroad employee.

A.M., 16 years old, male, a Mexican farmer, first became ill in February 1943. Syphilis and tuberculosis tests were negative. Tobacco or alcohol were not used. Asthmatoïd wheezing could be heard at a distance from the patient. Six months later nonproductive cough appeared at night. The next month the cough became productive; the sputum was copious, green and occasionally tinged with blood. His condition improved slightly during the next four months, but suddenly he returned and decided to enter the Hospital General of Mexico City. General examination revealed a pneumonic process of the left lower lobe. All laboratory examinations pointed to a general infection. Endoscopic examination of the patient showed the nose and pharynx normal, congestion and slight thickening of the vocal cords, trachea and right bronchus normal, partial stenosis of the lower bronchus on the left side giving the appearance of fibrosis following chronic swelling. Aspiration by insertion of the aspirating tube as far as possible in the different segments of the lower left lobe was performed. The bacteriological and cytological examinations revealed the ordinary type of common coccidial infection. This bronchoscopic examination was followed by



instillation of a solution of penicillin. Afterwards, the general condition of the patient improved enough to let him leave the hospital.

Two years later he returned to the hospital with the same symptoms and in addition fever and a great amount of purulent sputum. Clinical and x-ray findings revealed stenosis of the lower left bronchus and bronchiectasis of the corresponding lobe. He was referred to me and the endoscopic examination gave the following results: evidence of rhinoscleroma of the nose, swelling of the vocal cords, a large tumor mass located at the entrance of the left lower bronchus with infiltration of the mucous membrane, obstructing the lumen almost entirely. The tumor was removed and biopsy specimens taken from the infiltrated tissue. Drainage and aspiration completed the bronchoscopy. The pathologist reported the nature of the lesions as rhinoscleromatous. A very slight improvement of the patient's condition was noticed. Dr. Vergara then performed a successful lobectomy. The patient left the hospital and returned to his own place to continue his duties as a farmer. He has been well for almost two years.

*Comment.* The general conception that scleroma of the lower respiratory tract is secondary to rhinoscleroma in the upper air passages could not be positively confirmed. The last case might speak in favor of primary bronchial scleroma. It is true that when the patient was observed for the first time, the nature of the lesion was not proved, though its appearance did not leave in my mind any doubt about the diagnosis. It is remarkable that in the nose there was no vestige of disease when he was first observed. The existence of microscopic rhinoscleroma could be accepted, but, how many times in cases of proved rhinoscleroma have the trachea and bronchi not been inspected?

Undoubtedly, if the diagnosis of bronchial scleroma is full of interest, the treatment of this disease is not less interesting. My experience with streptomycin has not been sufficient to warrant a true evaluation of its efficacy. Radiotherapy, which gives wonderful results in rhinoscleroma and in certain cases of laryngeal scleroma, has failed in my series of cases of bronchial scleroma. So far, I believe that surgery endoscopically or by external method is the best that can be offered. Dilatation is very helpful during the phase of fibrosis. However, in spite of all known treatments, there are recurrences. Continuous revision and treatment is the destiny of patients suffering this terrible disease.

BUCARELI, 85.

HEMOPTYSIS SECONDARY TO CHRONIC MEDIASTINAL  
VENOUS OBSTRUCTION

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The exact cause and source of bleeding in a large percentage of patients with hemoptysis are often perplexing to the bronchologist. The object of this report is to direct attention to the circulatory disturbances incident to pathological conditions in the mediastinum as etiologic factors in obscure bronchial or pulmonary hemorrhage.

The bronchial arteries are usually described as three in number, one for the right lung and two for the left lung. The right bronchial artery varies somewhat in its origin and may arise either from the first or third intercostal artery, the right internal mammary artery or the right subclavian artery. The two left bronchial arteries usually arise from the ventral side of the upper thoracic aorta. Occasionally all three arteries stem from a common trunk on the thoracic aorta.<sup>1</sup>

The bronchial veins do not correspond closely to the bronchial arteries and are not found on the walls of the smallest bronchi. They arise from the first two dividing points of the bronchial tree, the tributaries uniting at the hilum of the lung into two small trunks; those of the right side open into the azygos vein and those of the left side into the hemiazygos or one of the intercostal veins.

The amount of blood supplied to the lungs by the bronchial arteries in a normal individual is said to be small. Fine ramifications of these vessels break up into a capillary network in the region of the terminal bronchioles.<sup>1</sup> Most of the blood from the bronchial arteries is returned via the pulmonary veins, an important exception being the areas about the hilum and the larger bronchi where the bronchial veins are fully developed.

The question of the relationship between the bronchial and the pulmonary arterial systems has undergone extensive study by anatomists. The consensus has been that in normal individuals the two systems are independent, aside from capillary anastomoses. Until recently, much less attention has been given to changes in one

system resulting from pathological alterations in the other. Wood and Miller,<sup>2</sup> by injection experiments, were able to demonstrate marked changes in the bronchial arteries in primary lung tumors, cardiovascular diseases and chronic tuberculosis. Dilatation, tortuosity and numerous bronchial-pulmonary arterial anastomoses were clearly shown. Deitrick and his co-workers,<sup>3</sup> attempting to obtain a satisfactory explanation for the hemoptysis occurring in mitral stenosis, also employed injection methods in autopsy specimens and reported marked dilatation of submucosal bronchial veins. They postulated that rupture or ulceration of these engorged vessels might be responsible for hemoptysis and likened the process to the massive bleeding from esophageal varices. Critical evaluation of this report would seem to raise some doubt as to the accuracy of the injection technique, but the investigation has raised a number of interesting possibilities.

#### REPORT OF CASES

CASE 1.—D. S., a 30-year-old white male, entered Presbyterian Hospital in January 1947, with symptoms of dyspnea for 18 months, cyanosis of the face and hands for many years, substernal oppression for six months and episodes of gross hemoptysis for four months.

His health had been good until the onset of dyspnea 18 months previously. In August he had been ill with a fever of 102.6° F. and general malaise. He was told that he had a fungus infection of the lungs, a diagnosis said to have been based on clinical findings. In October 1946 he began to cough up a teaspoonful or more of bright red blood two or three times daily. Hemoptysis became more severe in November and December and he was admitted to a tuberculosis sanatorium. Following a bronchoscopic examination, he was told that he did not have tuberculosis but that there was a growth in the right side of his chest. A second bronchoscopy, two weeks after the first, revealed that the growth had enlarged considerably in this short interval. He was then referred to Presbyterian Hospital.

The significant data in the past history were: (1) an account of having been gassed in a coke oven in a steel plant during the summer of 1946, with a brief period of unconsciousness, and (2) a history of a temporary blood pressure elevation (175/100 mm. Hg.) in October 1946.

*Examination:* Physical examination revealed a sturdy patient whose pulse, respirations and temperature were normal. The blood

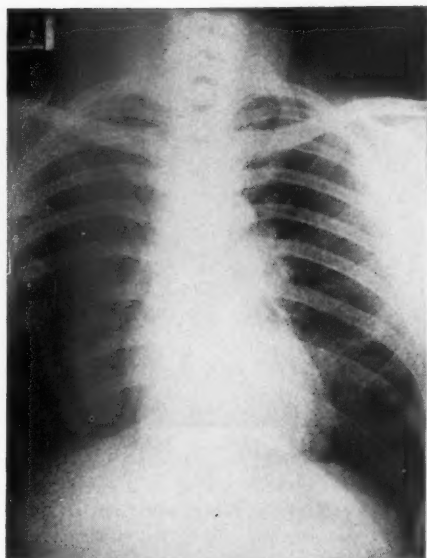


Fig. 1, Case 1.—Roentgenogram illustrating the shadow in the left hilar region. At operation a mass of dilated, engorged, tortuous blood vessels was found in this location.

count was normal, the blood pressure 110/50 mm. of mercury. The face and upper extremities were definitely cyanotic. He exhibited no dyspnea while lying in bed. There was marked clubbing of the finger tips.

There were dilated subcutaneous vessels along the anterior costal margins and a palpable inspiratory thrill over the right thorax posteriorly and inferiorly. There was increased bronchial breathing over all areas and especially over the right lung. An asthmatoïd wheeze was occasionally audible.

Roentgenograms were reported as showing a shadow in the left hilar region suggestive of a primary tumor (Fig. 1). Fluoroscopy of the esophagus after barium ingestion was negative.

Bronchoscopic examination on two occasions disclosed a marked widening of the tracheal bifurcation, bleeding from both main bronchi and external compression of the right main bronchus in its distal portion. The resulting narrowing obscured the middle and

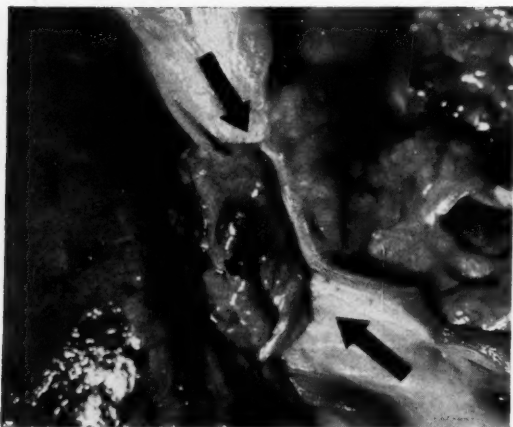


Fig. 2, Case 1.—Autopsy specimen showing encirclement and obliteration of the superior vena cava by a hyalinized calcified mass. Arrows lie in the nonobstructed part of the lumen and point to the stenosed region.

lower lobe subdivision. No intraluminal neoplasm was observed. Biopsies of specimens from the widened carina were negative. Lipiodol studies confirmed the carinal widening and the right bronchial compression.

Venous pressure readings in both antecubital fossae were between 23 cm. and 27 cm. of water (normal is 4 cm. to 14 cm. of water), while femoral venous pressures were 7 to 8 cm. of water. Blood pressure determinations in all extremities were normal and similar. Consultation with Dr. Earle Gray yielded the opinion that the circulatory disturbance was extracardiac. The electrocardiogram was normal.

A clinical diagnosis of superior vena caval obstruction was entertained and plans were made by Dr. J. M. Dorsey to perform a right thoracotomy.

*Operation:* Because of the left hilar shadow and the patient's insistence that his hemoptysis was always preceded by a gurgling sensation on the left side, a last minute change was made and exploration of the left chest was performed. The pleural space was free and no tumor mass was palpable in the left lung. The intercostal veins, the accessory azygos, hemiazygos and left phrenic veins

were quite dilated and comprised the mass which had been seen roentgenographically as a left hilar shadow. It was decided that nothing could be accomplished through the left chest and the wound was closed with the intention of exploring the right side at a later date.

On the fourth postoperative day the patient had several episodes of gross hemoptysis varying from 30 cc. to 180 cc. He became progressively cyanotic and expired the same evening.

*Necropsy Findings—Gross:* The right pleural space was almost completely obliterated by an old, healed generalized pleuritis. The phrenic, azygos, hemiazygos, intercostal, innominate, subclavian and internal mammary veins were markedly distended and dilated.

The superior vena cava, 2.5 cm. from its entrance into the right auricle, was completely occluded by an encircling calcified scarred mass. The encircling cuff was 2 cm. in diameter and 3 cm. long and was part of another mass lying beneath the superior vena cava, intimately associated with the right main bronchus and measuring 3 x 5 cm. Another similar connecting mass measuring 4 x 2.5 cm. lay beneath the tracheal bifurcation. On cut sections both masses were found to be calcified lymph nodes with caseous centers (Fig. 2).

The pulmonary veins were dissected out and found to be patent. The entire bronchial tree was filled with blood. The bronchial mucosa appeared normal. Sections of the lung disclosed markedly dilated vessels and many small hemorrhagic areas measuring 3 x 4 mm. in diameter.

There was evidence of venous congestion of the liver, markedly dilated splenic veins and numerous moderately severe esophageal varices. The remainder of the gross examination was not remarkable.

*Microscopic—*The mass which occluded the superior vena cava was composed of fibrous tissue, hyalinized fibrous tissue and calcium deposits (Fig. 3). With special stains no acid-fast bacilli were noted. Similar changes were observed in sections through the fibro-caseous mass beneath the carina and the right main bronchus.

In sections of right lung parenchyma there were several small, caseous tuberculous nodules in the visceral pleura. Blood was present about the smaller bronchi and bronchioles. The blood vessels adjacent to the bronchi showed marked thickening and intimal reduplication (Fig. 4). The peribronchiolar hemorrhage and the

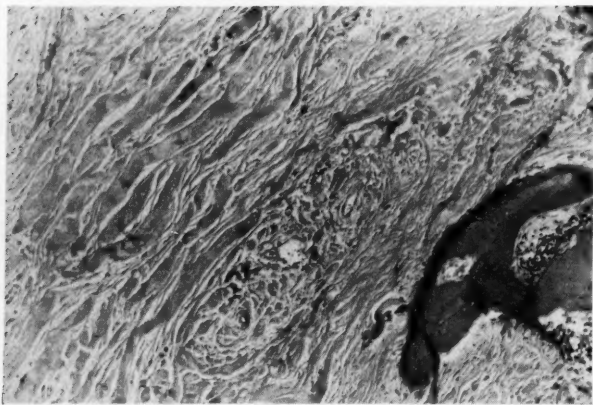


Fig. 3, Case 1.—Microscopic section showing hyalinized fibrous tissue and a fragment of bone from mass shown in Fig. 2.

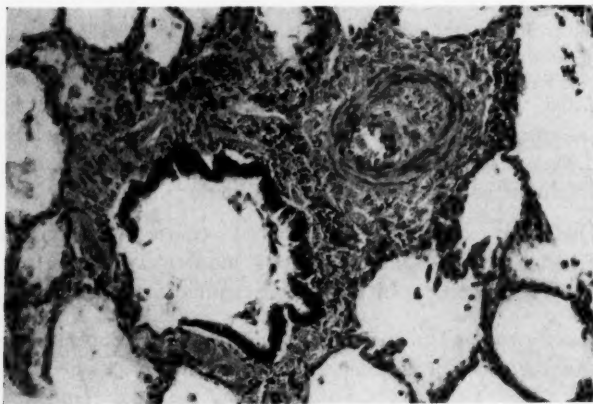


Fig. 4, Case 1.—Section of small bronchus and adjacent artery. Note the extreme degree of thickening of the vascular wall and the small residual lumen.



thickened vascular walls seemed logical sequences to the increased venous pressure which existed in the bronchial veins as a result of the superior vena caval occlusion.

*Comment:* A number of excellent reviews of the superior vena caval syndrome have appeared in recent years. Renewed interest in the subject has lately been stimulated by the development of phlebography, venous pressure determinations and measurements of circulation time.

Ochsner and Dixon<sup>4</sup> list the underlying etiological factors of superior vena caval thrombosis, in order of frequency, as syphilis, tuberculosis, cardiac disease, pyogenic infections and trauma. In a series of 27 verified cases of superior vena caval syndrome reported by Hussey, Katz and Yates,<sup>5</sup> all were due either to aortic aneurysm or malignant neoplasms. Osler's<sup>6</sup> classification of thrombosis due to disease within the vein or disease without the vein includes examples of all of the above types of pathological conditions.

The more prominent symptoms and signs such as dilated veins, dyspnea, cough, edema, cyanosis and chest pain need only be mentioned. Epistaxis has often been described but the problem of hemoptysis on the basis of the circulatory disturbance in this syndrome does not appear to have aroused much interest. The symptom was present in eight patients of one of the above series<sup>5</sup> but in all of these it was held to be due to a malignant neoplasm. Ochsner<sup>4</sup> refers to the infrequent occurrence of hemoptysis and mentions the possibility of mediastinal lesions exerting pressure on the pulmonary vessels and producing stasis in the lung parenchyma.

Milles<sup>7</sup> case report is similar in many respects to the one herein presented. He concludes that mediastinal tuberculosis in adults offers almost insurmountable diagnostic difficulties when the pulmonary tuberculous involvement is slight or absent. It must be thought of as a possibility in obscure mediastinal pathological conditions.

In our patient the superior vena caval obstruction predisposed to the development of collateral circulation in the bronchial veins by virtue of stasis and passive congestion in the azygos system. This collateral distention was of sufficient degree to produce a hilar shadow roentgenographically. The hemorrhages which occurred were too severe to be explained by mere capillary diapedesis. Gross and microscopic peribronchial bleeding, both recent and old, would seem to point to an analogy between this phenomenon and that seen elsewhere in the body in extreme passive congestion. Abnormal com-

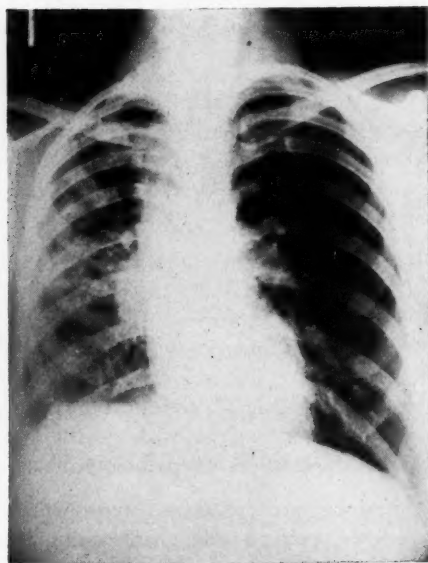


Fig. 5, Case 2.—Roentgenogram illustrating elevation and tenting of right diaphragm, diffuse mottling of the right lung, displacement of the heart and mediastinum to the right and a shadow in the right hilar region.

munications between the bronchial and pulmonary circulations doubtless existed, as evidenced by the uniform thickening of the walls of all vascular structures within the lung.

CASE 2.—H. H., a white married female, aged 36, was first admitted to Presbyterian Hospital, Chicago, in November 1946. There had been persistent bleeding from the mouth for the previous 14 years. The patient was uncertain whether the blood came from the respiratory or digestive tracts since its appearance was rapid and unheralded and the precipitating factors were so varied. Episodes of bleeding occurred three or four times daily, with amounts varying from a few flecks to a cupful or more. There were occasional latent periods of two or three months. Cough had not been a prominent symptom at any time, nor had there ever been any purulent sputum. Quick postural changes, emotional disturbances, fever, laughing, coughing or vomiting would usually cause bleeding. Wheezing respiration had first been noted just prior to admission.

There were no known etiological factors antedating her symptoms. Numerous roentgenograms, sputum and blood cultures had been made in another city. Bronchoscopy had not been performed.

*Examination:* Despite the prolonged and frequent blood loss, this patient appeared to be in good physical condition. The blood picture, gastro-intestinal tract and cardiac system were entirely normal. There was no evidence of sinusitis. Roentgenograms of the chest showed an elevation of the right diaphragm, increased lung markings on the right with a shift of the heart and mediastinum to that side, thickened pleura and a questionable area of increased density at the right hilum. An obstruction of the right main bronchus was suggested (Fig. 5).

Bronchoscopy disclosed a marked widening of the tracheal bifurcation with abnormal tissue in the proximal portion of the right main bronchus. This extended downward for a short distance until there was complete obstruction. When biopsy specimens were taken, the bleeding was profuse and alarming. A tentative diagnosis of bronchial adenoma was made.

Microscopic study revealed extremely dense scar tissue adjacent to cartilage from the bronchial wall. The pathologist's report mentioned that scarring of this type suggested proximity to an old tuberculous lymph node which had partially eroded the wall of the bronchus (Fig. 6). On the basis of this report it was decided to observe the patient.

The patient was next seen two months later. There had been no hemoptysis since the bronchoscopy. All laboratory tests for tuberculosis had meanwhile proven negative. She received treatment for a functional bowel disturbance and was again discharged.

*Subsequent Course:* In June 1947 there occurred the first episode of hemoptysis since the preceding November. However, the patient had noticed increasing dyspnea, cough and an asthmatoïd wheeze, the latter being accentuated by reclining on the right side. Bronchoscopy was again performed, this time with general anesthesia and preparations for blood replacement. The tracheal bifurcation was extremely difficult to identify because of neoplastic-appearing tissue which completely occluded the orifice of the right main bronchus. Biopsy removal caused immediate and brisk bleeding. Tissue removal was continued despite the bleeding until the lumen of the right main bronchus could be definitely discerned. At this point thick purulent secretion escaped from the previously blocked lung. At the conclusion of the procedure there was free passage of air from

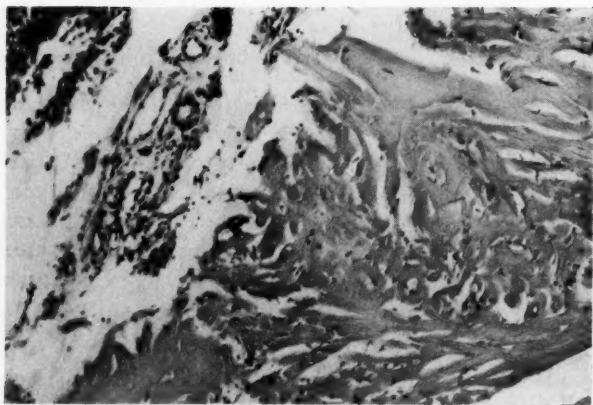


Fig. 6, Case 2.—Characteristic section of tissue obtained on biopsy of the obstructing mass in the right main bronchus. Note the extensive hyalinization.

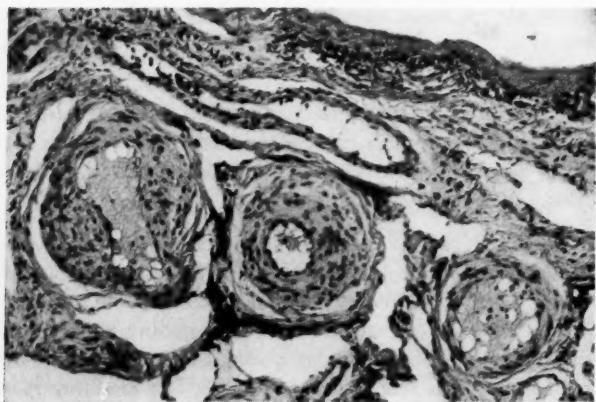


Fig. 7, Case 2.—Section from pleural margin of the excised lung. There are three dilated veins, the walls of which are markedly thickened. Anthracotic pigment may be seen in the perivascular lymphatics.

the right main bronchus although this structure was markedly narrowed.

Microscopic studies showed metaplasia of the bronchial epithelium, chronic granulation tissue in the subepithelial layer and masses of hyalinized fibrous tissue. The suggestion was again made that these changes were associated with a tuberculous peribronchial lymph node.

Lipiodol bronchograms were characterized by widening of the carina, normal filling of the right upper lobe and extreme narrowing of the right main bronchus beginning just below the upper lobe orifice. There was slight bronchiectasis of the middle and lower lobes. Pneumonectomy was decided upon.

A third bronchoscopy in July 1947 disclosed persistence of the abnormal tissue in the right main bronchus with only an eccentrically situated small lumen at 11 o'clock. Bleeding was again profuse.

*Operation:* At operation (Dr. J. M. Dorsey) there was an extensive fibrous pleuritis. After the lung had been freed, a sizable calcified mass was found completely investing the hilar structures and rendering impossible the identification of the pulmonary artery and vein. The azygos vein was divided near its entrance into the superior vena cava, the latter structure being to some degree involved in the hilar mass. The right lung was removed as close to the hilum as possible. Bleeding was profuse throughout the procedure, and seven pints of blood were administered during the operation.

*Pathologic Examination—Gross:* Study of the excised lung revealed that it had apparently been removed at the level of secondary or tertiary bronchi. These bronchi were only slightly larger than normal and there were occasional small dilatations in their course. There was no tumor tissue. The lung was firm in consistency. No abscesses were noted.

*Microscopic:* There was extensive thickening of the alveolar walls due to an increase in the amount of fibrous connective tissue. The walls of the medium-sized arteries and veins were conspicuously thickened, with a moderate degree of intimal reduplication (Fig. 7). The pathological diagnoses were: interstitial fibrous pneumonitis, severe; bronchiectasis of the right lung, slight; dilatation and hypertrophy of the bronchial and pulmonary blood vessels; pulmonary anthracosis and hemosiderosis.

The patient left the hospital, 25 days after surgery, in August 1947. There was a short febrile episode several weeks later, presumably the result of overactivity upon her return home. This subsided and she has remained symptom-free to date.

*Comment.*—An exact diagnosis of this patient's disease cannot be readily established. There was evidence of encroachment upon the trachea and right main bronchus by tissue resembling a healed tuberculous lymph node. At operation a calcified mass was found at the hilum, investing the large vessels and rendering impossible a complete removal of the lung. The bleeding encountered both at bronchoscopy and thoracotomy indicated a high venous pressure. Microscopic examination of the excised lung revealed marked thickening of all the blood vessel walls, indicating the probable presence of some type of bronchopulmonary anastomoses.

Jackson and Diamond<sup>8</sup> have mentioned the long-standing hemoptysis which may occur in bronchiectasis. The findings of bronchiectasis in this patient were surprisingly minimal and not at all proportionate to either the duration or the character of her symptoms. It will be recalled that cough was not present except for a short time prior to surgery, whereas the bleeding had persisted for 14 years.

The pathological process was fortunately not of sufficient extent to produce obstruction of the superior vena cava. Ligation of the azygos vein and removal of the greater portion of the right lung, which had become fibrosed following prolonged passive congestion, have resulted in an arrest of symptoms. It remains to be seen whether the calcified mediastinal mass will cause any further trouble.

#### SUMMARY AND CONCLUSIONS

The case histories of two patients with hemoptysis of an unusual type have been presented.

In one patient there was obliteration of the superior vena cava by an inactive calcified tuberculous mass. Passive congestion in the bronchial venous system and resulting abnormal bronchopulmonary circulatory anastomoses are thought to have been the principal factors responsible for hemoptysis.

In the second patient, the tissue obtained bronchoscopically on several occasions suggested its proximity to a tuberculous lymph node. A calcified hilar mass obstructing the pulmonary vessels and partially involving the superior vena cava was found at operation.

Right pneumonectomy has thus far resulted in an apparent cure of long-standing hemoptysis.

Attention is directed to the role of mediastinal pathology and secondary bronchopulmonary passive congestion in the etiology of obscure pulmonary hemorrhage.

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## GRANULOMA OF LARYNX FOLLOWING ENDOTRACHEAL ANESTHESIA

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WATERVILLE, MAINE

Despite the large number of anesthetics administered endotracheally each year few cases of complications due to laryngeal trauma have been reported. Three cases, those of Clausen,<sup>1</sup> Gould<sup>2</sup> and Cohen,<sup>3</sup> appeared in the British literature in 1932, 1935 and 1938, respectively. In this country Smiley<sup>4</sup> (1940), Farrior<sup>5</sup> (1942), Kearney<sup>6</sup> (1946) and Tuft and Ratner<sup>7</sup> (1947) have each reported a case, while Barton<sup>8</sup> (1947) added two to the list. One other case has been reported by McLaurin<sup>9</sup> this year, making a total of ten.

Because of the infrequency of granuloma of the larynx following endotracheal anesthesia, the following case is presented.

Mr. J. H. D., aged 40, was referred because of hoarseness and laryngeal obstruction noted on exertion. Five months before he had undergone a two-stage lumbar dorsal splanchnicectomy under endotracheal anesthesia in another hospital. The anesthesia time for the first stage was five hours; for the second stage, four hours. A soft rubber No. 32 catheter had been used, inserted with a stylet. Hoarseness developed two months later. I had had the opportunity of seeing this patient sometime before and had found a normal larynx on routine examination.

Examination now revealed the posterior portion of the glottis obstructed by what appeared to be granulomata. One sessile granuloma covered the posterior third of the right vocal cord and was superimposed upon a larger, partially pedunculated mass extending forward to the middle third of the left cord (Fig. 1).

Under local anesthesia (1% pontocaine solution) the larynx was exposed with the anterior commissure laryngoscope and the growths removed with cup forceps. The histopathological report confirmed the diagnosis of granuloma (Fig. 2).

The patient was discharged from the hospital and did not report again for three months. At this time the left cord, the site of

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From Thayer Hospital.



Fig. 1.—Schematic drawing of the larynx showing a direct laryngoscopic view of a granulomatous tumor originating from the region of the vocal process of the right arytenoid. This type of tumor usually springs from the bed of a previously ulcerated cord area.

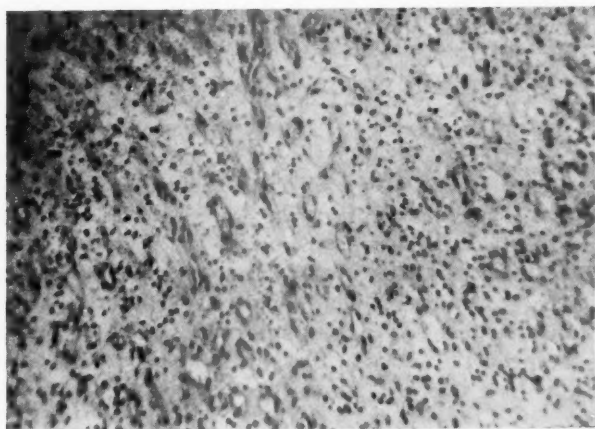


Fig. 2.—Histological section from tumor-like granuloma showing large capillary spaces filled with blood with a surrounding basic structure of scar tissue. In some areas where the capillaries have become obliterated, the vascular spaces have become converted into a nonvascular mass of scar tissue.

the larger underlying tumor, was healed but a small granuloma about 2 mm. in diameter was noted on the right cord. This was removed in a manner similar to the first procedure. His subsequent course was uneventful and examination now shows a normal appearing larynx.

Kearney stated that this type of tumor tends to become pedunculated. Inasmuch as this would allow easier removal with less resulting raw surface, he advised waiting for this to take place before operating, provided the airway remained adequate. This view is concurred in by McLaurin, whose experience with the sessile granuloma was similar to mine.

In my case five months had elapsed and the airway obviously was inadequate and, according to the patient, becoming progressively worse, which condition made an operation necessary. Perhaps removal of the larger pedunculated granuloma alone would have been preferable at that stage, but the position of the uppermost tumor made this seemingly impossible. While conclusions cannot be drawn from the scanty material available, it would seem that the pedunculated granuloma has little tendency to recur while the sessile type may require multiple removals. Therefore, if conditions permit and the airway is adequate, one might well keep such a patient under observation in the expectation that the growths would become pedunculated.

The fact that so few cases have been observed would indicate that laryngeal trauma is not a common occurrence following intubation for anesthesia. Apparently the length of operation plays little part, for while in many of the reports it was fairly long, in McLaurin's case it was only 45 minutes. The consensus of opinion seems to be that the process starts as a traumatic ulcer of the cord exposing the vocal process. This might occur from too large a tube or one which was allowed to move up and down, possibly from motion of the patient's head or neck, producing repeated irritation on the cord.

The infrequency of occurrence certainly suggests no criticism of this form of anesthesia but merely that every patient developing hoarseness be examined with the possibility of granuloma in mind. The suggestion of Barton that the larynx be examined following every endotracheal anesthesia, and appropriate treatment applied to any abrasions, merits consideration.

PROFESSIONAL BUILDING.

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## Abstracts of Current Articles

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### EAR

#### **Per-Operative Audiometry; Evaluation on the Operating Table of the Primary Gain, in the Course of Fenestration.**

Aubry, M.: *Les Annales D'Oto-Laryng.* 64:642-647 (Nov.-Dec.) 1947.

The author presents some interesting audiometric results, taken on a number of patients, before, during, and after the fenestration operation. It is worthy of note that the gain in hearing acuity becomes manifest as soon as the labyrinth is opened. It is greatest for the lower and middle frequencies, ranging from 12 to 20 decibels. The hearing was tested four to six weeks postoperatively, and a further gain of about five decibels was found in the lower and middle frequencies.

The author describes the technical problems involved in obtaining these audiometric readings during the operation and tells how many were solved.

HARKINS.

#### **Otitis Media in Infancy.**

Derham, R.: *Brit. Med. J.*, May 1, 1948, p. 835.

Of the 7,806 admissions to the Alder Hey Children's Hospital of Liverpool in 1946, 1,107 were infants under 12 months of age. Of these, 431 either had ear suppuration on admission or developed it during hospitalization. The treatment consisted of myringotomies, antrotomies with or without the use of penicillin or chemotherapy. Of the 431 infants, 163 died, a mortality rate of 38 per cent. There was no great difference in the results of myringotomies and posterior drainage. Penicillin appears to have only a small place in the treatment of otitis media in young infants. The mortality rate is high in spite of treatment with sulfonamides, penicillin and intravenous fluids.

GROVE.

**Mastoid Surgery—Old and New.**

*Tumarkin, A.: The Lancet, May 8, 1948.*

Otologists used to do radical mastoid surgery to save life. We should do radical mastoid surgery to save hearing. This problem is particularly important in children of the poorer classes, among whom bilateral otitis media is only too prevalent. Chronic suppurative otitis media is usually benign; about 80 per cent of the cases can be cured by conservative treatment. For the remaining 20 per cent Tumarkin proposes an operation which he calls a transmeatal attico-antrotomy. During the past 12 years he has performed 300 such operations and finds them much more satisfactory than the radical mastoid operation.

The incision begins at Shrapnell's membrane and curves up to the roof of the osseous external canal. It then passes outward and backward and finally downward demarcating a tiny semi-oval flap. This is elevated and rolled out of the way on the floor of the meatus, exposing the outer attic wall. As this bone is removed the incus and stapes come into view. In favorable cases nothing more need be done, but if the incus and malleus are diseased they must be removed. Diseased cells extending in various directions from the antrum are easily followed and cleaned out. The operation is completed by rolling the skin flap into place in the floor of the cavity. Epithelization is usually complete in three to six weeks.

The advantages of the operation are: 1.) It starts in the diseased area. 2.) The skin flap is about half the size of a postage stamp, the soft tissues are hardly disturbed at all and the operation is almost bloodless. 3.) The bone excision is minimal and the operative cavity small. The cavity heals rapidly and prevents the long-continued suppuration so often seen after a radical operation. 4.) The functional results of the operation are excellent. 5.) The operative scar is invisible. 6.) Convalescence is short and after-treatment minimal and painless. The first dressing is done in seven to ten days and twice weekly thereafter. This is important in children who dread the usually painful dressings.

The attico-antrotomy operation is not designed to excise all diseased tissue but rather as a drainage operation to be performed at any early stage. Emphasis is placed upon preservation of function rather than a quest for an improbable outlying infected cell. As long as the surgeon makes an adequate exposure of the attic, antrum and aditus he may expect a higher percentage of satisfactory results than by any other method.

In his own series of over 300 cases Tumarkin has had no deaths or infections of the brain or the lateral sinus. Three patients developed a transitory facial palsy. One patient developed labyrinthitis which was cured by penicillin.

Tumarkin recently reviewed 50 consecutive cases. He received 42 replies. Thirty-eight of the 42 mastoid cavities were completely healed and dry. These were not mild or early cases. Fourteen patients had had intermittent otorrhea for over 20 years. Only one case was under a year's duration. The remainder had had discharging ears for 3 to 20 years.

GROVE.

**Penicillin Therapy in Scarlet Fever and Complicating Otitis.**

*Torben, Jersild: The Lancet, May 1, 1948.*

Since December 1945 all scarlet fever patients in the Blegdam Hospital have been treated with penicillin. All patients admitted on one day were given penicillin and those admitted on the following day sulfanilamide and so on until 200 had been treated with penicillin and 200 with sulfanilamide. Children under 1 year received 40,000 units of penicillin three times a day; children aged 1 to 5 years, 60,000 units, children 5 to 15 years, 80,000 units; and adults, 100,000 units for six days. Since October 1, 1946, 350 patients have been treated with penicillin in the above dosages, and 142 patients have been given penicillin twice daily for six days, the dosage being 60,000, 90,000 120,000 and 150,000 in the above-mentioned four age groups. These patients were as a rule discharged from the hospital in six to eight days.

Of the sulfanilamide-treated patients, 73 per cent still harbored hemolytic streptococci at the end of treatment and complications appeared in 49.5 per cent of this group. On the other hand, in the penicillin-treated patients only 4 per cent still harbored hemolytic streptococci at the end of treatment and complications appeared in only 5.5 per cent of this group, there being no cases of otitis or nephritis.

To find out how soon hemolytic streptococci disappeared from the nasopharynx, cultures were made every four hours on 32 patients. Eighteen of these were free of hemolytic streptococci as early as 12 hours from the beginning of penicillin treatment and on the third day all patients gave negative cultures. The strepto-



cocci disappeared from the ear discharge just as rapidly without any local treatment. The sore throat subsided more rapidly in penicillin-treated patients. In penicillin-treated patients the primary fever lasted 4 to 5 days. In the sulfanilamide group the average was 7 days. The rash was not influenced by the treatment.

They have now treated 1000 patients with penicillin and in not one did nephritis or secondary otitis develop.

In 1946 25 patients with scarlatinal otitis were treated with penicillin. In all of these the ear discharge was free of streptococci in 24 hours except three in which the discharge became sterile in three days. In this group only two required a mastoid operation and in one of these the mastoiditis was already present on admission. During the same period 65 patients with scarlatinal otitis were treated with sulfanilamide and of these 35 per cent required mastoidectomy.

GROVE.

#### **The Working of a Hearing Aid Clinic.**

*Stevenson, R. Scott: Brit. Med. J., May 22, 1948, p. 990.*

In 1937 the Metropolitan Ear, Nose and Throat Hospital of which Stevenson was a staff member started a Hearing Aid Clinic. In 1945 when after the war years the hospital resumed its normal peacetime activities, the Hearing Aid Clinic was reorganized with a staff of one full-time audiometrist and one trainee. Each patient is first examined by an otologist who takes the history, makes a routine ear, nose and throat examination, tuning fork, voice and whisper tests. The patient is then sent to the Hearing Aid Clinic which is in operation every day of the week from 9:30 a. m. to 5:00 p. m. The fitting of hearing aids is done in an ordinary, quiet room with furniture in it and not in a bare soundproof room. The audiometricians are especially trained at the hospital. For audiometricians they do not use nurses, largely because of the shortage of nurses, but rather intelligent, well-educated (high school class) young women of the medical secretarial class. They are given a six months' course of training, at the end of which they must pass an examination on the basic principles of anatomy and physiology of the ear, the basic principles of acoustics, the physics of audiometers and hearing aids and their mechanisms, the psychology of the deaf, the handling of deaf mute children, and the principles of lip read-

ing. They are not allowed to fit hearing aids except under the guidance of a regular medical practitioner.

The Clinic believes that when the audiometer shows a 30 to 40-decibel loss over the speech frequency range, an aid should be fitted and this aid should give a gain in speech reception of at least 50 decibels. At this clinic it is believed that although an aid which gives a uniform gain for all frequencies is generally applicable, the low and the high frequencies often have to be boosted in the amplification of the aid. The Clinic has a "library" of instruments which are on the approved list of the National Institute for the Deaf. The audiometricians are instructed while giving every possible help in the selection of a proper aid to leave the final choice up to the patient, it being bad psychology to force any particular aid on a patient. A "difficult" patient may be referred to a medical psychologist associated with the Clinic. It is a rule of the Clinic that all patients who have been fitted with a hearing aid must be referred to a teacher of lip reading.

The time required for the entire examination and fitting of the hearing aid varies from one to two hours. In spite of this and the care exercised in the fitting of the aids a surprisingly large number of aids are returned after a week's trial.

In 1946, 355 electrical aids were recommended and 170 of them were returned; 120 non-electrical aids were recommended and 62 of them returned. In 1947, 778 electrical aids were recommended of which 256 were returned; 53 non-electrical aids of which 28 were returned. Stevenson believes that the main reason for the return of so many aids is their initial expense and the high cost of upkeep. He believes that if more time could be spent in training the hearing aid wearer in its use, fewer would be turned in.

GROVE.

## LARYNX

### Case of Sarcoma of the Larynx.

Broughton-Barnes, E., Duthrie, E. S., Jolles, B.: *Brit. Med. J.*, June 26, 1948.

Quoting statistics of Havens and Parkhill, New, Ewing, Jackson and Coates, Thomson and Colledge and Clerf, the authors come to the conclusion that sarcomata of the larynx are quite rare and probably do not constitute more than one per cent of all laryn-

geal malignancies. Sarcoma of the larynx is a localized tumor with very little infiltrative power, often pedunculated, less often sessile or lobulated. The site of predilection is the true vocal cord. Metastases are uncommon and recurrences even more uncommon. These tumors are usually larger than carcinomata. Hoarseness is the predominant symptom. Dysphagia is rare although in two of the cases described by Figi in 1933 an emergency tracheotomy was necessary. Histologically, fibrosarcoma, chondrosarcoma, fibromyxosarcoma and rhabdomyosarcoma can be distinguished. The treatment is surgical and laryngofissure is adequate. Prognosis is relatively good.

The authors report a case of a male, 66 years of age, with hoarseness of several weeks' duration. A tumor of the right cord was found and removed by diathermy. The pathological diagnosis was sarcoma, probably fibromyxosarcoma. Six months later there was a recurrence at which time a laryngofissure was done. Post-operatively, deep x-ray treatment was given. Four years later the patient was well and there had been no recurrence. The larynx was of normal appearance except for a slight thickening of the right vocal cord.

GROVE.

### MISCELLANEOUS

#### Comparative Studies of Several Antihistaminic Drugs.

Arbesman, C. E.: *J. Allergy* 19:178, 1948.

Obtaining his data from a series of 291 patients, the author compared the relative efficacy of five common antihistaminic drugs. His patients received various combinations of two antihistaminic drugs, and the results are compared. The author found that Pyribenzamine was most efficacious for inhalant allergic rhinitis; Neoantergan, Hydryllin, Neohetramine and Antistine, in that order, were less helpful.

Similarly, Hydryllin was most effective for extrinsic bronchial asthma; Pyribenzamine, Neoantergan, Antistine and Neohetramine, in that order, gave less symptomatic relief.

Where one drug fails to give relief or has severe side effects, another antihistaminic drug might be satisfactory.

The side reactions usually attributed to antihistaminic drugs occurred with all of the drugs used. Hydryllin and Neoantergan

caused the highest percentage of side effects, and Neohetramine and Antistine the lowest, but the latter two drugs gave a higher percentage of severe side effects.

Although Hydryllin was the most helpful of the drugs used for bronchial asthma, it was not as effective as epinephrine or large doses of Aminophyllin.

BICKMORE.

#### Facial Paralysis of Unknown Origin.

*Tello, A. T.; Rec. de Otorrlaryng. 7:127-138 (Dec.) 1947.*

The author has recorded his findings in ten cases of facial paralysis of unknown origin.

His thesis is the relationship between this condition and other diseases, such as poliomyelitis and encephalitis, which are characterized by paralysis and known to be caused by virus infection.

He presents evidence that the cochlear and vestibular nerves and the spinal fluid are also affected by the disease. Cochlear involvement is manifested by hypoacusis which is contrary to the belief that hyperacusis is occasionally present. The vestibular reactions are described as "alterations in the excitability of the canals." The changes in the spinal fluid are not constant but of great importance. In two cases there were positive globulin tests. The lymphocyte count was generally increased. In one case it reached 290 per mm.

He distinguishes two clinical forms of the disease: one in which the facial, cochlear and vestibular involvement are all manifested and clear up spontaneously; and the other in which the facial nerve recovers but the hypoacusis, abnormal reactions of the canals and the elevated spinal count persist. These may be the earliest signs of a disease which will later spread to other structures. Patients with this form of the disease should be kept under observation.

His conclusions are that facial paralysis of unknown origin may be an unrecognized form of poliomyelitis or caused by a specific virus which has a predilection for the ganglia of the seventh and eighth nerves.

HIGBEE.

**A Case of a Complete Fistula of the Thyro-Glossal Duct, Having an Intra-Hyoid Tract.**

*Montauffier and Chassagnette: Les Annales D'Oto-Laryng. 65:168-170 (March-April) 1948.*

A case is reported of an eight-year-old child having a patent thyroglossal duct fistula. The external opening of the fistula was situated in the midline of the neck, two finger-breadths above the manubrium of the sternum. The orifice was very small and led upward into a subcutaneous pouch (the size of a hazelnut) lying in front of the thyroid cartilage. This pouch was attached to the upper tip of the pyramidal lobe of the thyroid gland. The tract continued upward to the hyoid bone as a thick-walled structure. It then penetrated tangentially through the hyoid bone, going in through the lower ventral aspect and emerging through the upper ventral aspect on this bone. The upper end of the fistula was the foramen cecum.

The entire fistulous tract was dissected out, including the central portion of the hyoid bone, with uneventful healing of the wound.

The authors place emphasis upon the fact that the tract does not pass dorsally to the hyoid bone, but passes into and out of this bone through its ventral aspect.

HARKINS.

**The Present Status of Pulmonary Resection for Carcinoma and Inflammatory Diseases of the Lung.**

*Gale, J. W., and Currevi, A. R.: Wisconsin M. J. 47:210-213 (Feb.) 1948.*

Carcinoma of the lung accounts for about 10 per cent of all malignant growths. It is encountered five times as frequently in men as in women. Eighty per cent of the lesions are found in the larger bronchi near the hilum. The onset is insidious but soon certain signs point to a lesion of the respiratory tract. These are (1) cough, present in 70 per cent of the cases, (2) hemoptysis; in about 60 per cent of the cases it may appear very early, (3) pain; this occurs in about 50 per cent of the cases and is usually deep-seated and dull in character. Frequently the localization of the site of the pain localizes in lesion. (4) Weight loss may occur early.

It is sometimes difficult to make an early diagnosis. A careful history is important but a physical examination of the chest may

reveal very little in the early stages. Other tests are listed in the order of their importance:

1. Roentgenograms. These should be made in anteroposterior, lateral and oblique positions.
2. Bronchoscopy. Since many carcinomata appear in the large bronchi in the neighborhood of the hilum they can often be visualized and a biopsy specimen taken.
3. Sputum. Special stains may sometimes show the presence of cancer cells.
4. Exploratory thoracotomy. This should be reserved for those patients in whom all other tests fail to establish a diagnosis.

The only logical treatment when diagnosis has once been established is complete removal of the lung on the affected side together with the mediastinal lymph nodes.

*Bronchiectasis.*—Roentgenograms in several views, lipiodol filling of all the lobes and bronchoscopy are all necessary adjuncts to a physical examination and history.

The treatment of bronchiectasis is twofold, conservative and surgical. Conservative measures are too numerous to mention and are, for the most part, grossly ineffective. Probably the most valuable nonsurgical treatment is postural drainage. The authors state that this often fails because it is improperly carried out and give directions for the correct method of procedure.

Surgical procedures such as artificial pneumothorax, oleothorax, plombage and thoracoplasty are mentioned only to be condemned. Phrenectomy may give relief but the operation of choice is lobectomy. This may include the removal of one or more lobes in one stage. Three of the five lobes have been successfully removed. Preoperatively postural drainage is used vigorously, accompanied by aerosol penicillin and streptomycin. In the last two years the authors have performed lobectomies on 33 patients with a mortality of 9 per cent.

*Abscess and Gangrene.*—The authors in common with others consider both of these as the same clinical entity since they are both tissue-destroying, necrotizing processes. Many abscesses heal spontaneously and are unrecognized. If the patient survives the acute stage, two courses may ensue: spontaneous cure or a chronic infection. The diagnosis of the chronic stage is not usually difficult. Bronchoscopy assists in ruling out a foreign body or a new growth. Bronchography seldom helps in the diagnosis.

For many years the treatment of chronic lung abscess has consisted of different types of surgical drainage. The authors feel that lobectomy is the proper method of treatment because (1) it insures complete ablation of the diseased process, (2) it eliminates the possibility of complications such as air emboli, brain abscess, hemorrhage, secondary plastic operations and recurrence, (3) it often happens that with peripheral processes beyond the vision of the bronchoscope there is a new growth or foreign body of which the abscess is a complication, (4) the lung parenchyma and bronchi surrounding the abscess are eliminated as a source of continued suppuration and toxemia and (5) the mortality is lower. In the last two years the authors have performed 10 lobectomies for this condition with a mortality of 10 per cent.

In the last two years the authors have performed resection in 34 cases of pulmonary tuberculosis with no mortality. Most of these operations were performed in otherwise hopeless cases.

GROVE.



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